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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

APRIL 1938

THE PASTEUR-MEYERHOF REACTION IN MUSCLE METABOLISM

Harvey Lecture, November 18, 1937

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BEFORE ENTERING on my subject, may I say that this title is not quite adequate. The Pasteur-Meyerhof reaction is the main subject of my lecture, but it is my intention at the same time to deal with the metabolism of the aerobically working muscles on a somewhat broader basis than indicated by the title.

It is an assumption frequently encountered in physiological literature, that the metabolism of the aerobically working muscles is a pure carbohydrate metabolism. That assumption cannot have originated from the experience gained in metabolism determinations during muscular exercise. It is a familiar fact that even heavy muscular exercise can be performed on a pure fat diet, and with a respiratory quotient which indicates a combustion almost entirely of fat. Experiments by Krogh and Lindhard[1], and recently by their pupils[2,3], have demonstrated this very convincingly. Of course, the fact that hard muscular work can be performed under conditions in which the respiratory quotient is low, does not disprove the belief

that the working muscles oxidize carbohydrate only; for the possibility certainly exists that in the organism—presumably in the liver—there is a process of carbohydrate formation from fat, so that the muscles may very well be supplied with carbohydrate even in conditions in which the organism as a whole is metabolizing fat alone. However, this purely hypothetical possibility can scarcely explain why the conception of a pure carbohydrate metabolism in the aerobically working muscles is so hard to eradicate, as actually seems to be the case. From this remark perhaps you will anticipate that I think that this conception should be discarded.

If we endeavor to discover how such a conception arose, and whence it has obtained sustenance all this time, we shall quickly find that the conception of a pure carbohydrate metabolism in the striated muscles arises from, and is supported by, the experience gained in experiments on the chemistry of isolated muscles, mainly the isolated muscles of cold-blooded animals.

The first to make convincing demonstrations of the connection between the mechanical function of muscles and a production of lactic acid, i.e., a carbohydrate metabolism, were Fletcher and Hopkins[4]. At this juncture, however, perhaps I may be permitted to say that probably the first to express the supposition of a connection between a formation of lactic acid in the muscles and their work was the Swedish chemist Berzelius. Du Bois-Reymond[5] tells us that in 1841 Berzelius stated that he had noticed that muscles from animals which had been hunted before being killed, seemed to contain very considerable quantities of lactic acid, whereas muscles from partly paralyzed extremities seemed to contain only small quantities of that substance. Nevertheless, it was of course the famous investigations of Fletcher and Hopkins[4] that brought lactic acid formation into the prominent position in muscle chemistry which it has since preserved almost intact. Their experiments showed how lactic acid, which had accumulated in muscle during work, would disappear after the work when the muscle was kept under aerobic conditions. However, the explanation of the disappearance of the lactic acid under aerobic conditions stands to the credit of Meyerhof[6], from whose fine experiments it appeared, that under aerobic conditions lactic acid can be rebuilt into the glycogen from which it was originally formed. In forming an estimate of the value of these investigations, admirable as they are in themselves in their more general biological applicability, it must be remembered that the direct demonstration of the resynthesis of glycogen from lactic acid

can be made only under conditions in which the formation and the removal of the lactic acid are separated in time. Finally, it must be borne in mind that, judging from these experiments—on cold-blooded animals only, it is true—the resynthesis of lactic acid to glycogen seems to be a fairly slow process. It is now easy to see why Meyerhof's demonstration of a carbohydrate cycle: glycogen⇌lactic acid has become generalized, in the sense that such a cycle has been accepted as an explanation both of the so-called Pasteur reaction in yeast, and of the parallel circumstance that no lactic acid formation can be demonstrated in aerobically working muscles. If the theory should be maintained that a breakdown of glycogen to lactic acid is an absolutely essential phase in the chemistry of muscle contraction, it would become absolutely necessary to assume that a formation of lactic acid does take place also in aerobically working muscles; indeed a lactic acid formation of the same degree as that taking place in a muscle which, under anaerobic conditions, works with the same intensity. In actual fact, the entire conception of the central rôle of lactic acid in the chemistry of muscle contraction only became possible when Meyerhof's demonstration of the carbohydrate cycle permitted the assumption that the reason why no lactic acid formation can be demonstrated in an aerobically working muscle is, that the lactic acid actually formed is rebuilt into glycogen as quickly as it is formed. That the theory concerning the rôle of lactic acid formation in muscle contraction (for which Meyerhof fought, and especially in his controversy with Embden fought so energetically) necessitated this interpretation of the Pasteur-Meyerhof reaction in the muscles, and thereby made the same interpretation of the Pasteur reaction in yeast probable, is undoubtedly the psychological reason why this interpretation was accepted without hesitation. For actually, the direct proofs of the correctness of this view are not strong.

By the Pasteur reaction is understood, as you know, the circumstance that under aerobic conditions fermentation recedes, in some cases completely, so that the yeast has a metabolism that is purely oxidative. As far as we can see, Pasteur himself conceived fermentation and oxidation as two mutually independent metabolic processes, in the sense that they are not coupled processes, but two reactions which can replace each other. Nowhere does Pasteur express the supposition that the cause of the recession of fermentation under aerobic conditions is that the terminal products of the fermentation process, or intermediate products, are resynthesized into carbohydrate. That interpretation is Meyerhof's[6].

That the so-called oxidation coefficient, or the Meyerhof coefficient, is of fairly constant value, has been regarded as evidence that Meyerhof's interpretation of the mechanism of the Pasteur reaction is correct, that is, as evidence of a coupling between oxidation and resynthesis into carbohydrate. By the oxidation coefficient is understood the ratio between the recession of the fermentation or glycolysis under aerobic conditions and the oxidation intensity. The determination of this coefficient is of course of value only, when it concerns yeast or tissues in which a residue of the fermentation or glycolysis persists under aerobic conditions. It must be pointed out, however, that this coefficient displays nothing like pronounced constancy. And in those cases in which there has been an assumption that a conformity exists between the oxidation coefficient in yeast and tumor tissue, and the oxidation coefficient in muscle, it must be pointed out that no such conformity has been proved. The oxidation coefficient for muscle has been calculated on the basis of experiments on the directly demonstrable resynthesis of lactic acid to glycogen in muscle which, after having worked anaerobically, is supplied with oxygen. In the first place, the ratio found in such experiments between "disappeared lactic acid" and oxidation (oxygen consumed during restoration) is not at all constant; and in the second place, the question of how the basal metabolism of the muscle in the very long period of recovery is to be accounted for in the calculation is a most uncertain one. Finally, it must be pointed out, and that is perhaps the most important point, that the calculations are made on the supposition that the resynthesis of lactic acid is the only endothermic reaction in recovering muscles in which the oxidation energy is engaged, whereas we now know that other endothermic reactions take place (resynthesis of creatine phosphoric acid). All in all, it must be said that the postulated constancy of the oxidation coefficient in various tissues does not contain any demonstrable evidence that the Pasteur-Meyerhof reaction depends upon a coupling between a resynthesis of carbohydrates on the one hand, and oxidations on the other.

It has been asserted that the correctness of Meyerhof's interpretation of the mechanism of the Pasteur-Meyerhof reaction is proved by Meyerhof's experiments with yeast[7], the object of which was to show more directly an oxidative resynthesis to carbohydrate of the final product of the fermentation process, alcohol. Thus these experiments would correspond exactly with the demonstration of the oxidative resynthesis of lactic

acid to glycogen in muscles during aerobic recovery. Whereas in Meyerhof's muscle experiments[6] it has been possible to show directly an increase of the glycogen content in the muscles, proceeding in equal pace with the disappearance of the lactic acid, no corresponding direct demonstration has been made of an increase of the carbohydrate content in yeast respiring in an alcoholic medium. On the other hand, Meyerhof[7] under such conditions found a very low respiratory quotient, the respiratory quotient when yeast oxidizes alcohol usually being as low as 0.3. Meyerhof took this low quotient to be evidence of a resynthesis of carbohydrate, a reaction having the character of a partial oxidation and therefore bound to give a low respiratory quotient. From the respiratory quotient Meyerhof calculated the ratio between oxidized and resynthesized alcohol, that is to say the "oxidation coefficient", and found that it was of the same value as the oxidation coefficients in yeast calculated in other ways and the corresponding coefficients in tumor tissue and muscle.

I have made experiments of the same kind[8], and have been in a position to confirm the regular occurrence of very low respiratory quotients when yeast respires in alcoholic medium; at the same time, however, I consider I have been able to show that Meyerhof's interpretation of these very low quotients is incorrect.

If a moderate quantity of alcohol is employed in the medium, and the experiments are continued for some hours, it will be found that in the first periods the respiratory quotient is very low. At a certain point of time, dependent on the amount of alcohol added to the samples, the respiratory quotient rises quickly, rather suddenly and reaches unity. It can now be shown that as long as the respiratory quotient remains low, an organic acid accumulates in the samples, and, when the quotient rises, the organic acid begins to disappear while simultaneously the intensity of oxygen absorption begins to decrease. If the experiments are discontinued at a time when alcohol still remains in the samples, it is possible by direct alcohol determinations to establish the amount of alcohol that disappeared during the experimental period. From the carbon dioxide output and the directly determined acid formation (determined as increase in ether-soluble acids), it is possible to calculate the total amount of alcohol oxidized completely and that oxidized to organic acid. If the sum of these two values is compared with the directly determined loss of alcohol, we find that the latter is somewhat greater than the sum of the other two values. Thus some alcohol seems to have disappeared which cannot be

accounted for, and which consequently may have been converted into carbohydrate. This quantity, however, is much smaller in proportion to the alcohol oxidation than that calculated by Meyerhof. The latter calculated the ratio between alcohol resynthesized into carbohydrate and alcohol oxidized at 3 : 1; according to my experiments the ratio cannot be more than 1 : 1, that is to say a ratio of dimensions quite different from the oxidation coefficient found previously. There can be no doubt that the very low respiratory quotients are mainly a result of the fact that alcohol is oxidized by yeast in two phases, the alcohol first being converted into organic acids (presumably acetic acid), which thereupon are oxidized completely.

TABLE I

	CO_2 cmm	O_2 cmm	RQ	*Alcohol completely oxidized* mg%	*Alcohol oxidized to acid* mg%	*Alcohol disappeared calculated* mg%	*Alcohol disappeared determined* mg%	*Alcohol oxidized to carbohydrate* mg%
POISONED SAMPLES								
Exp. 1	93	280	0,33	9,5	21,1	30,6	31	0
" 2	72	289	0,25	7,4	29,0	36,4	34	—2,4
" 3	85	288	0,30	8,7	27,6	36,3	33	—3,3
" 4	116	348	0,33	11,9	23,6	34,5	38	3,5
" 5	117	338	0,35	12,0	24,4	36,4	33	—3,4
NORMAL SAMPLES								
Exp. 1	167	499	0,34	17,1	22,1	39,2	56	16,8
" 2	178	500	0,36	17,8	23,4	41,2	58	16,9
" 3	173	495	0,35	17,7	25,8	43,5	56	12,5
" 4	130	349	0,38	13,3	14,7	28,0	38	10,0
" 5	138	372	0,37	14,1	17,0	31,1	35?	3,9?

As I attach some importance to these experiments I shall take the liberty of going into them a little further and showing you some of the numerical data. The experiments were carried out partly with normal yeast and partly with yeast poisoned with iodo-acetic acid, whereby the ability of the yeast to ferment is destroyed. In table 1 you see the results of five experiments with normal yeast and five with poisoned yeast. The last column contains the calculated formation of carbohydrate. You will observe that in the poisoned samples, which by the way have a rather lower oxygen absorption than the normal samples, there is no evidence of any carbohydrate formation, whereas in the normal samples there is. The ratio of alcohol oxidized to alcohol resynthesized appears from a comparison between the fourth and the last column. There is no difference, how-

ever, in the respiratory quotient in the two series of experiments. Thus we may say that the respiratory quotient in the normal samples does not appear to reflect any carbohydrate synthesis. Only when we make the rather complicated calculation, the elements of which are the output of carbon dioxide, the alcohol determinations and those of the ether-soluble acids, is any carbohydrate formation revealed. In advance it was reasonable to assume that there would be no carbohydrate formation, at any rate in yeast poisoned with iodo-acetic acid, and no such formation could in fact be demonstrated. Therefore, the consequence of the close agreement between the value of the respiratory quotient and its variations in experiments with normal and poisoned yeast is, that we cannot feel fully convinced that carbohydrates really are formed in the normal samples.

TABLE II

	Poisoned			Normal		
	cmm CO_2	*cmm* O_2	*RQ.*	*cmm* CO_2	*cmm* O_2	*RQ.*
0 min. to 30 min.	37	114	0,32	39	112	0,35
35 min. to 1 hr. 05 min.	25	110	0,23	44	132	0,33
1 hr. 10 min. to 1 hr. 40 min.	29	101	0,29	61	150	0,41
1 " 45 " " 2 " 15 "	43	80	0,54	84	86	0,98
2 " 20 " " 2 " 50 "	47	55	0,86	76	76	1,00
2 " 55 " " 3 " 25 "	40	43	0,93	30	29	1,03
3 " 30 " " 4 " 00 "	40	41	0,98	21	21	1,00
4 " 00 " " 4 " 30 "	31	33	0,94	9	9	1,00
4 " 30 " " 5 " 00 "	28	27	1,03	8	8	1,00
5 " 00 " " 5 " 30 "	16	15	1,05			
5 " 30 " " 6 " 00 "	8	8	1,00			

In table 2 I have shown the results of two experiments with normal and poisoned yeast, continued so long that the alcohol disappeared entirely; the oxidation intensity has fallen to the same low values as are found for yeast suspended in pure phosphate buffer. In other words, the experiments were continued till the samples were practically free of substrate. You will observe that the quotient rises through the experiment—rather more gradually in the poisoned sample than in the normal one. If we calculate the quotient for the total experimental period we get 0.54 for the poisoned sample and 0.59 for the normal one, that is to say, quotients that are rather below the quotient for a pure alcohol oxidation, but of almost equal size in the two samples. Were the reduction of the quotient due to a formation of carbohydrate, the latter would, according to these experiments, in which the calculation is not very complicated, be just as pronounced in

the poisoned sample as in the normal. There is nothing to show that the organic acid in the normal sample passes through a conversion to carbohydrate before being completely oxidized. I therefore consider that my experiments entitle me to conclude that, even if one cannot definitively deny the possibility of a synthesis of alcohol to carbohydrate, no real evidence can be produced to show that such a process does occur. If a synthesis of alcohol to carbohydrate does occur, at any rate the oxidation quotient of that process has a value quite different from the one Meyerhof[7] calculated, and from the one which can be calculated on the oxidation intensity and the recession of the fermentation when yeast respires in carbohydrated medium. Consequently, nothing in these experiments tends to show that Meyerhof's interpretation of the mechanism of the Pasteur-Meyerhof reaction is correct, and therefore there is some justification in asking if there is any reason for continuing to accept that interpretation.

You will recollect my saying that Meyerhof's interpretation was, so to speak, necessary if the conception of lactic acid formation as an essential part of the chemistry of muscle contraction were to be maintained. Here again it is not possible today to discern any reason for persisting in this interpretation.

At the present moment it is doubtless generally acknowledged that the formation of lactic acid is not essential to the chemistry of muscle contraction. I believe there is reason for saying that the introduction of iodo-acetic acid poisoning in muscle chemistry has contributed very considerably to the rapid and complete acceptance of that view.

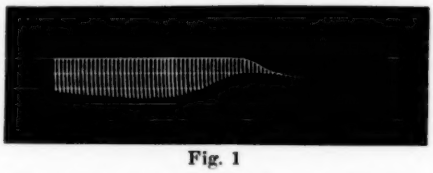

Fig. 1

Typical series of isometric twitches performed by a gastrocnemius muscle poisoned with iodo-acetic acid. Muscle weight: 0,7 g. Distance between two horizontal lines: 200 g. tension.

Though for obvious reasons the investigations on the chemical changes in working muscle poisoned with iodo-acetic acid holds a favorite place in my heart, on this occasion I shall deal only briefly with the results achieved from the experiments[9,10].

The effect of iodo-acetic acid is an inactivation of the enzyme system involved in the formation of lactic acid. A muscle poisoned with this compound is capable of performing a series of 60-90 twitches anaerobically without any formation of lactic acid taking place and then goes into rigor (Figure 1). The twitches are in all respects completely normal, that is in respect of latent time, duration of the twitch, heat formation, development of tension and action current. The total amount of work which an isolated poisoned muscle is able to perform is, however, smaller than that which a normal one can perform. This may be expressed by saying that the energy reserve available under anaerobic conditions is decreased when the ability to form lactic acid is abolished. These facts alone give a clear conception of the rôle played by the formation of lactic acid in the chemistry of muscle contraction. The formation of lactic acid is not a necessary link in that chemistry, and consequently this process cannot have any direct connection with what we may call the mechanism of contraction. On the other hand, the formation of lactic acid or the ability to form lactic acid must be looked upon as an important energy reserve available under anaerobic conditions.

When we determine the chemical changes occurring in an iodo-acetic poisoned muscle during stimulation, we find that the intensity of the breakdown of creatine phosphoric acid is greater than in a normal muscle. When a poisoned muscle has performed a series of 60-90 twitches the muscle is exhausted and goes into rigor. At this stage the total amount of creatine-phosphoric acid has been broken down, and, moreover, the adenylic phosphoric acid has been broken down too. In a normal muscle only about one-third of the creatine phosphoric acid has been broken down after the performance of 60-90 twitches. The energy liberated during the anaerobic work of a poisoned muscle undoubtedly originates from the breakdown of creatine phosphoric acid. Having regard to the time I have at my disposal I shall not venture upon a discussion of this statement.

There is one point, however, elucidated through my experiments with muscle poisoned with iodo-acetic acid, which I would like to deal with more fully, as it is of essential importance to the subject of my lecture today.

When two symmetrical sartorii, which have been poisoned by soaking in Ringer solution to which iodo-acetic acid has been added, are stimulated, one in oxygen and the other in nitrogen, it is seen that the muscle

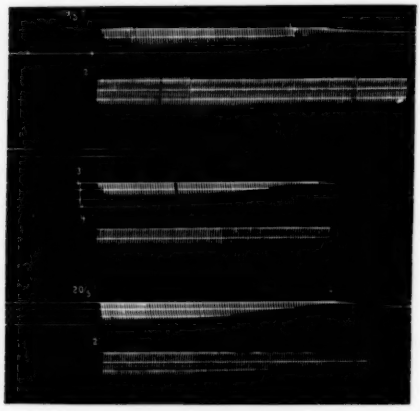

Fig. 2

Series of isometric twitches performed by symmetrical IAA-poisoned sartorii muscles, one stimulated in nitrogen (upper ones) and one stimulated in oxygen (lower ones).

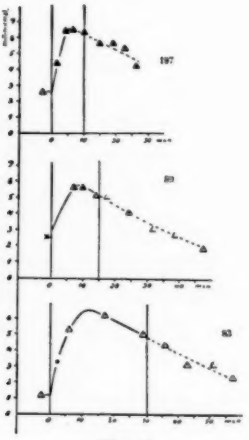

Fig. 3

Changes in blood lactate concentration during and after muscular exercise. Duration of work indicated by interval between the two vertical lines. Working intensity in all experiments 900 kgm/min.

supplied with oxygen is capable of performing much more work than the muscle stimulated in nitrogen. The latter will be completely exhausted and go into rigor at a time when the other muscle is still giving maximum tension. This is illustrated by these records, from experiments of the kind I have described (Figure 2). If the muscle which has worked aerobically is analyzed at a point of time when it has performed a much greater work than the completely exhausted anaerobic muscle, it will be found still to contain considerable quantities of creatine phosphoric acid. This means that there can be no doubt that energy arising from oxidation processes can be utilized in the production of mechanical energy, that is to say, utilized for the performance of exterior work, even under circumstances where there can be no question of intermediate lactic acid formation. That such a formation is out of the question, may be concluded with certainty from the fact that the symmetric muscle, working under anaerobic conditions, passes through the series of twitches in a manner characteristic of a muscle completely poisoned with iodo-acetic acid.

We cannot say with certainty whether under these circumstances the oxidation energy is utilized through an oxidative resynthesis of creatine phosphoric acid, or is transferred more directly to what we may call

"the mechanism of contraction". As long as it has not been shown that the breakdown of creatine phosphoric acid is not a necessary link in the chemistry of muscular contraction, I shall consider it most natural to assume that the oxidation energy is utilized through an oxidative resynthesis of creatine phosphoric acid; but perhaps the day is not far distant when it will be possible to show that the breakdown of creatine phosphoric acid is not an obligatory process in the chemistry of muscle contraction, just as it has been possible to show this as far as lactic acid formation is concerned.

To my mind the following conclusions are justified from the results obtained in experiments with muscles poisoned with iodo-acetic acid.

The formation of lactic acid is not an essential element in the chemistry of muscle contraction, nor is an intermediate lactic acid formation a necessary element in the utilization of oxidation energy for the production of mechanical energy in the muscles.

Accordingly, the experience gained in experiments with isolated muscle no longer provides a reason for assuming that in aerobically working muscle there is a constant intermediate formation of lactic acid which, as quickly as it is formed, is resynthesized to glycogen. Another way of expressing this is, that no reasons can be found for accepting Meyerhof's interpretation of the Pasteur-Meyerhof reaction in aerobically working muscles. On the other hand we can still speak of a Pasteur-Meyerhof reaction in aerobically working muscles, as by this we merely understand the circumstance that the formation of lactic acid decreases in the muscles under aerobic conditions.

The question may now be asked: If we cannot accept the factors which originally supported the "classic" view of the Pasteur-Meyerhof reaction in the striated muscles, then are there any others to be advanced in favor of that view? I do not think so.

There are experiments on the blood lactic acid concentration in man during and after muscular exercise, and these experiments to my mind rather argue against the classic view of aerobic muscle metabolism. Experiments of this kind were made by O. Bang[11], partly in Krogh's institute and partly in mine.

By means of a micro-method, which makes it possible to measure the lactate concentration in blood samples of only 0.1 cc., Bang has followed the variations in the blood lactate concentration during and after exercise. Thanks to the method employed, the concentration could be deter-

mined at short intervals, whereby a reliable curve was obtained for the variations. As far as the present subject is concerned, greatest interest attaches to those experiments in which the working intensity was such that a "steady state" was quickly arrived at. Figure 3 shows three curves from such experiments. It will be seen that immediately after the commencement of the exercise the blood lactate rises quickly and reaches a maximum in the course of from seven to ten minutes. Then the concentration begins to fall, even when the work is continued. This means, then, that even under conditions in which a steady state is arrived at for oxygen absorption, this does not happen with the lactic acid concentration, at any rate, not in the blood. In experiments in which the working intensity is less, and the primary increase of the blood lactate is consequently lower, the blood lactate falls even to basal values during the work. Even if we cannot assume that the blood lactate at any moment reflects the concentration in the working muscles, the falling blood curves to me are incompatible with the conception of a high, constant level in the working muscles throughout the working period. This applies especially to the experiments in which the blood lactate fell to basal values during the work. Now, this high and constant level is necessary if the classic view of the metabolism of the aerobically working muscles is to be upheld. According to that view, the assumed constant lactic acid production was supposed to lead in relatively few minutes to the attainment of a constant, increased lactate level in the active muscles, subsequently maintained throughout the "steady state". The constant level, it was thought, was attained by the rise in lactate concentration in itself inducing a rise in the intensity of oxidation, which in turn would involve a rise in the lactate resynthesis, until an equilibrium was established between production and resynthesis, at a level depending on the intensity of lactic acid formation, i.e., the intensity of work.

It is an outstanding feature of the curves in Figure 3 that the fall in blood lactate continues steadily after cessation of the work. This is difficult to reconcile with the conception that during work a very intensive production of lactic acid proceeds in the active muscles, but that this ceases simultaneously with the work. In that case one would expect to find a much quicker fall after work ceased. In reality, however, the three curves are almost identical, although they represent experiments with varying periods of work. The working intensity, on the other hand, was the same in all three experiments.

Personally, I am inclined to believe that Bang's interpretation of the experiments may be correct. According to Bang[11], we must assume that an intensive formation of lactic acid takes place in the active muscles in the first minutes after the commencement of work. Presumably the reason is that it takes a certain time for the general and local circulations to adapt themselves to the increased demand for oxygen. Until the circulation is adjusted, the muscles work partly anaerobically; that is to say they utilize the anaerobically available energy depôt represented by the ability to form lactic acid. When the circulation is adjusted and the oxygen supply to the muscles is adequate, all formation of lactic acid ceases. Thus, at the commencement of work a depôt of lactic acid is formed in the active muscles. The size of this depôt is independent of the duration of the work, and solely dependent on the intensity of the work. The greater the intensity of the work, the greater quantity of lactic acid can be formed before the circulation has become adjusted.

However, even if there is much in favor of Bang's interpretation of the experiments, it must be said that not even that interpretation provides a fully satisfactory explanation of the circumstance that the fall of blood lactate continues steadily after cessation of work. The depôt of lactic acid which, according to Bang, is presumably formed in the active muscles during the first minutes of the work, must be imagined as being removed, partly by diffusion to the blood and from there to resting organs (principally the liver), partly by oxidation in the active muscles, and finally by resynthesis to glycogen in the active muscles. Whereas the latter process may well be a slow one, it is hard to understand that the oxidation of lactic acid in the active muscles does not proceed with considerable intensity, and especially with greater intensity during work, when metabolism is greatly increased, than after cessation of work. A dependence of the rate of lactic acid removal on the rate of metabolism actually has been demonstrated by Newman, Dill, Edwards and Webster[12].

For this reason the fact that the blood lactate concentration may fall and even reach the basal level during the working period must be considered the most clearcut and consequently the most important result of the determinations of the blood lactate concentration during muscular exercise. As already mentioned this observation is incompatible with the classic view, according to which the metabolism of aerobically working muscles includes an obligatory intermediate lactic acid formation, which is balanced by an oxidative resynthesis of the lactic acid formed.

If now we return to the theory of a pure carbohydrate metabolism in the active muscles, it must be said that we have been unable to find any support for that theory in the experimental facts to which I have so far referred. This is a matter of considerable weight, as it eliminates the basis on which the theory to my mind has principally rested.

As I have laid particular stress on Meyerhof's interpretation of the Pasteur-Meyerhof reaction as a basis for the theory of a pure carbohydrate oxidation in aerobically working muscles, I should state at the same time that this interpretation, as indeed pointed out by Meyerhof too, does not require as an inevitable consequence that the metabolism of the active muscles be a pure carbohydrate oxidation. There is the possibility that the energy necessary for the endothermic lactic acid synthesis is produced by the oxidation, not of lactic acid or carbohydrate, but of fat or protein. This, however, does not alter the fact that Meyerhof's interpretation of the Pasteur-Meyerhof reaction has been regarded, and justly so I think, as an argument in favor of the assumption that the aerobically working muscles oxidize carbohydrate only.

Personally, I am inclined to the opinion that under such conditions, in which a formation of lactic acid actually takes place in the active muscles, the effect is that the oxidation proceeds entirely, or principally, at the expense of carbohydrate. In muscle working partly anaerobically there will be simultaneously lactic acid formation and oxidation. With very intense muscular exercise, which can only continue for a short time, the muscles will work to an appreciable degree anaerobically, and under just such conditions we see respiratory quotients of about unity, even when the quotient in rest lies much lower. Exactly the same thing is seen in the untrained subject during moderate work. Here, too, the respiratory quotient rises and remains high during the work, and simultaneously the blood lactate curve rises steadily as a sign that the muscles are working under partly anaerobic conditions.

If it be true, as I am inclined to believe, that lactic acid formation in the active muscles always leads to a high respiratory quotient, that is to say, to a combustion of carbohydrate; then it must be said that the low respiratory quotients seen in well-trained individuals on a fat diet, even during the performance of heavy work, also indicate that lactic acid formation is no obligatory link in the metabolism of the active muscles.

In conclusion, I would refer to a matter which, to me, has been of no small importance in judging the question of whether there is reason for

assuming that the metabolism of the aerobically working muscles is of specific character. For if it is, the most natural conclusion to draw is that it is a pure carbohydrate metabolism.

What I have in mind in this connection is the fact that the intensity of alcohol oxidation is not affected by muscular exercise.

I admit that the question of whether muscular exercise affects the intensity of alcohol oxidation has been answered variously by different authors. Nevertheless, in recent years more and more have accepted the view that the question must be answered in the negative. Among the experimental results which seem to show that the intensity of alcohol oxidation is not increased during muscular exercise, those of Nyman and Palmlöv[13] are particularly convincing. As shown in experiments by Widmark[14] and others, however, the intensity of alcohol oxidation increases if metabolism is stimulated by dinitrophenol. This is also the case with thyroxin, according to Le Breton's preliminary experiments[15]. As alcohol oxidation represents up to 80 per cent of the basal metabolism, it would seem necessary to assume that part of the alcohol oxidation proceeds in the muscles. Therefore, the circumstance that an increased metabolism conditioned by muscular exercise does not increase the alcohol oxidation, whilst an increased metabolism produced by stimulating drugs does, seems to justify the conclusion that there is a specific difference between the metabolism of the resting muscles and that of the active muscles. In her monograph on alcohol oxidation Le Breton[15] actually arrives at a conclusion to this effect.

The circumstance that muscular exercise does not increase the intensity of alcohol oxidation might, however, have the explanation that neither in rest nor in work is alcohol metabolized directly in the muscles. If we imagine that alcohol oxidation is a specific function of the liver, it is easy to understand that an increased metabolism, due to an increased energy output in the muscles alone, does not increase the alcohol oxidation, whereas an increase of the metabolism intensity in all tissues, the liver included, does involve an increase of the alcohol oxidation.

One difficulty in assuming that oxidation of alcohol takes place only in the liver, is that the absolute quantity of alcohol oxidized in rest, as already stated, represents up to 80 per cent of the basal oxygen absorption, whereas in the liver the oxygen absorption amounts to only 30 or 40 per cent of the total basal oxygen absorption. Therefore, the assumption that alcohol oxidation is a specific liver function is conditional upon the

alcohol oxidation in the liver being a partial oxidation. A priori that idea cannot be dismissed, so much the more as partial oxidations are undoubtedly a characteristic feature in the metabolism of the liver. Even if we must also assume that the partially oxidized product formed in the liver is oxidized in all tissues, the muscles included; the primary oxidation in the liver will nevertheless be the limiting factor for the disappearance of alcohol in the whole system.

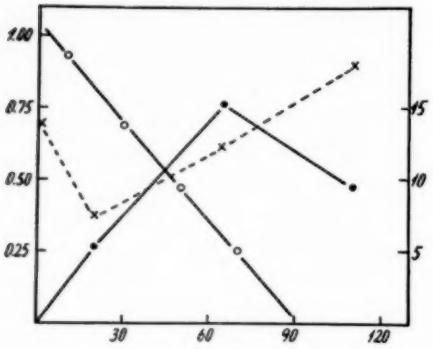

Fig. 4

Exp. on alcohol oxidation in isolated cat liver. Abscissas: time in minutes. Left ordinate: blood alcohol in per thousand and RQ. Right ordinate: decrease in alkali reserve in cc carbon dioxide.

o —— o blood alcohol

x ···· x R.Q.

● —— ● acid formation (decrease in alkali reserve)

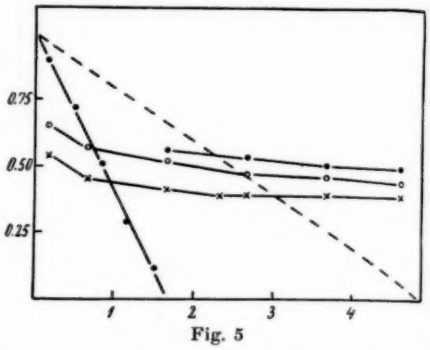

Fig. 5

Exps. on alcohol oxidation in isolated hind-limb preparations. Abscissas: time in hours. Ordinates: blood alcohol in per thousand.

The three curves from three different experiments on hind-limb preparations may be compared with a curve from an experiment on a liver (steep curve in the left part of the figure). As, however, the total amount of blood and tissue acting as solvent for the alcohol is three times as large in the hind-limb preparations as in the liver preparations, the curves from the experiments on hind-limb preparations actually must be compared with the broken curve.

That the supposition I have sketched is undoubtedly correct appears from certain experiments, as yet unpublished, which I have made on alcohol oxidation in artificially perfused isolated livers and hind-limb preparations. These experiments show that, in the liver, alcohol undergoes a rapid but primarily only partial oxidation, whereas alcohol is not affected oxidatively at all in a hind-limb preparation. I shall take the liberty of showing you one or two curves from these experiments.

From the curves (Figure 4) it will be seen that the concentration of alcohol in the blood which is perfused through a liver falls quickly and at quite a constant rate. In the course of ninety minutes the entire quantity of alcohol (300 mg.) has disappeared. The quantity of oxygen necessary to oxidize 300 mg. alcohol completely is 440 cc. The oxygen absorption in the first ninety minutes was only 225 cc. After adding the alcohol, the

respiratory quotient falls from 0.69 to 0.37. This extraordinarily low quotient can only be explained as being due to incomplete oxidation. The lack of conformity between the quantity of disappeared alcohol and the absorbed quantity of oxygen may be explained in the same manner. In addition, the alkali reserve of the blood falls as a sign that acid products are being formed. When the alcohol has almost disappeared from the blood the alkali reserve begins to increase again. At the same time the respiratory quotient also rises; in the last determination in this experiment it reaches a value of 0.9. The increase of both the alkali reserve and the respiratory quotient must be assumed to be the result of a complete oxidation of the partially oxidized acid products formed in the first period after adding the alcohol. Incidentally, the similarity between an experiment of this kind and the yeast experiments previously mentioned is very striking.

The acid product formed in the liver experiments was not isolated and identified, but there can hardly be any doubt but that it was acetic acid. As acetic acid oxidizes with great rapidity in the living organism, it may be assumed that the acetic acid formed in the liver of an intact animal after the addition of alcohol is carried with the blood to all the different tissues and oxidized there.

In an isolated hind-limb preparation, alcohol is not affected oxidatively at all. After diffusion balance is established we see only a very slow fall in the blood alcohol concentration, a fall which does not exceed that seen in control experiments, in which the blood is circulated through the apparatus without passing living tissue (Figure 5).

The absolute quantity of alcohol oxidized in an isolated liver, per gram of liver tissue and minute, averages no more than 60 per cent of the quantity oxidized in the entire animal per gram of liver tissue and minute. Probably the cause of this is that the oxygen consumption of the liver, that is to say the metabolism intensity, falls distinctly in the course of the first five or ten minutes after isolation, so that we must also assume that the alcohol oxidation in a liver in situ is greater than in an isolated liver. The dominating rôle played by the liver in alcohol oxidation also appears from the fact that in eviscerated animals, the alcohol oxidation is extremely low and does not exceed 10 per cent of that of intact animals.

Thus the assumption that the oxidative metabolism of the active muscles is of a specific nature cannot find support in the circumstance that the intensity of alcohol oxidation is not increased during muscular

exercise; for the explanation is that alcohol is only primarily affected oxidatively in the liver, so that it is the primary oxidation in the liver that becomes the limiting factor in the alcohol oxidation of the total organism.

As I have said, it may be assumed that the partially oxidized product formed in the liver can be oxidized completely in the various tissues, the muscles included. I point this out, even if at the moment I cannot submit direct experimental evidence of it, because I am inclined to think that the same applies to the oxidation of fatty acids. It is probable that the high-molecular fatty acids are not attacked, or not readily attacked oxidatively in the muscles. On the other hand, partly oxidized products of the fatty acids, such as β-hydroxybutyric acid and other ketone bodies, are very readily oxidized in the muscles. The fact that the oxidation of ketone bodies in the muscles is increased when the muscular metabolism is stimulated by work has been proved by experiments performed by Blixencrone-Moller in my institute. As these investigations have not yet been published I shall merely deal with them very broadly.

If a cat-liver with a high fat content and poor in glycogen is artificially perfused, that liver will yield very considerable quantities of ketone bodies to the blood. A liver from a cat which for some days has been treated with phloridzin, or a liver from a pancreatectomized cat, will in the course of two hours produce and transfer to the perfusion blood from 200 to 300 mg. of ketone bodies or even more. Now if such blood, which is rich in ketone bodies, is perfused through an isolated hind-limb preparation, the total quantity of ketone bodies will disappear in the course of one and one-half to two hours. This means that the quantity of ketone bodies capable of being formed by a liver, even under circumstances in which that formation is profuse, can be got rid of at a rate corresponding to the rate of formation in a mass of muscle representing less than half of the total muscle of the animal. If the experiment is performed so that the musculature of the hind-limb preparation is stimulated for a period of fifteen minutes, whereby the oxygen consumption of the preparation rises to about four times the basal consumption, all the ketone bodies will have disappeared in the course of only twenty to thirty minutes. Therefore it is not open to doubt that ketone bodies are utilized as a fuel in muscular exercise. It must be regarded as very improbable, not to say out of the question, that ketone bodies in an isolated muscle preparation are converted into carbohydrate before they are utilized.

The assumption that fat oxidation proceeds in such a manner that the fatty acids in the liver undergo a partial oxidation to β-hydroxybutyric acid, and that it is this partly oxidized product which is utilized in the muscles, provides a natural and plausible explanation of the circumstance that the efficiency in muscular exercise is lower with pure fat combustion than with chiefly carbohydrate combustion, as has been proved by Krogh and Lindhard[1].

In the course of this lecture I have referred to experimental results from very different fields within physiology: from research on the oxidative metabolism of yeast; from experiments with muscle poisoned by iodoacetic acid; the concentration of blood lactate in man during muscular exercise; the metabolism of alcohol in the organism; and the metabolism of fat in the isolated liver. To me, all these results, however different in nature they may seem, have been of significance in my consideration of the problem of the aerobic metabolism of muscle.

There is no doubt that this problem is capable of elucidation in many other and better ways. I have mainly quoted results from fields in which I myself have worked experimentally, and which therefore have played a very special part for me in my deliberations. In my opinion, all the various relations I have submitted to you are comformable, in that they contain no basis for the assumption that the aerobic metabolism of the active muscles is a pure carbohydrate metabolism; indeed, some of them are directly contradictory. It is possible that some of you share the view I have arrived at from this, that the aerobic metabolism of the active muscles is not a pure carbohydrate metabolism, whereas others do not. I scarcely imagine that I have convinced those who do not share my view, but it has been a source of great pleasure to me to have the opportunity of going so deeply into the considerations on which my opinion of the problem is founded.

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THE CONCEPTION OF CANCER BEFORE AND AFTER JOHANNES MÜLLER*

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IT IS becoming increasingly the vogue to commemorate centennials. There is frequently little true sentiment in these gestures; the centennial becomes an excuse for a celebration or for an exploitation. Too often the attitude is not that of reverence for great events of the past; instead, the past becomes only a convenient background against which the presumed progress of the present may be displayed by contrast. I mention this attitude because I venture to bring to you tonight the materials for a medical centennial, and I do not want my object or my attitude mistaken. Neither is in the vogue. I want, if I can, to revive the past and make it live just for a moment in some of the realities it possessed. And my attitude is that of an almost religious obeisance to one of the great men and one of the great events of medicine. Tonight I bring you nothing new but only the hope that in reviewing together here briefly the life of a man we may pause together in our busy ways of the present to revere his memory and to acknowledge a debt.

There have been men—and you can count their number on the fingers of your hands—who have taken up great boulders far beyond the strength of ordinary men and with them have laid down the foundation upon which medicine is erected. Johannes Müller was such a man. The reason that we might celebrate in his honor this particular year of 1938, and the reason for my paper tonight will become evident from a quotation that I read from his works. His words and his sentences as you will see form the foundation for the modern conception of the nature of cancerous growths. In quoting him I pick and choose only a few pertinent sentences from a dozen pages of his book entitled: "On the Nature and Structural Characteristics of Cancer and of those Morbid Growths Which may be Confounded with it." The book was published in 1838.

The first sentence I quote shows with pathetic clarity the lack then

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of any adequate means of differentiating malignant from non-malignant growths. Müller writes: "Usually it is regarded as an infallible sign of malignancy if a tumor, after having been extirpated once or twice, returns to the same spot."

As to the need of some better criterion he says: "All these circumstances, while they render it extremely easy to confound tumors naturally innocent and dangerous only under certain circumstances, with such as are by nature malignant, afford many additional reasons for seeking some surer means of distinguishing between the two than we at present possess."

He then goes on to say that the classification of morbid growths is wholly deficient; that there is literally none. As a first step toward clarifying the confusion he has made a collection of tumors at the Royal Museum of Berlin. Of this collection he says:

"On close inspection of the preparations, many were met with presenting such peculiarities that it was not possible to assign them any certain place in accordance with the state of knowledge at that time. Soon it became evident that if the classification of so many important objects were to have any real value, it would be necessary to devote many years to the examination of them and of other fresh pathological specimens; and to this task the author accordingly betook himself."

Müller next turned to his microscope to utilize the method that he was instrumental in introducing into pathology; he examined under the microscope the tissues in his collection.

He says: "As early as the year 1836 the author had recognized with the microscope the cellular nature of various morbid growths . . . the cells unless magnified from 400 to 500 times generally look like granules; but on the employment of a high power the cellular structure of most morbid growths becomes apparent."

He goes on further to say that the cellular form in a neoplasm resembles in general features that of the tissue in which the growth occurs. And then, and perhaps most important of all, he relates the cellular physiology of neoplasms to that universal for normal tissues. He says:

"The part which cells sustain in the composition of all morbid growths has recently acquired additional importance from the investigations of Schleiden and Schwann. The researches of the former relate to the development of the young cells of plants from nuclei formed in the interior of the parent cells; those of the latter refer to the analogy

between animal and vegetable structures. According to Schwann all tissues in the embryo are formed from cells, which are themselves developed from nuclei; the growth being the result of fresh formations of cells, which afterwards undergo transformation into other tissues. These observations . . ." (and I break my quotation here to mention, what I shall deal with more fully later, that Schwann was the pupil of Müller and made his investigations on the cell in Müller's laboratory and under Müller's inspiration). I continue: "These observations led the author to examine morbid growths very carefully. By employing a high magnifying power, cells were observed in malignant growths. . . . The nuclei of the cells were discovered . . . in many instances too, young cells were found. Thus, then, as might have been anticipated, did examination of morbid structures confirm Schwann's observations touching the development and growth of healthy tissues."

The statements which Johannes Müller makes are the beginning of the cellular pathology which his brilliant young pupil Virchow expanded during the next ten years into a basic concept. Johannes Müller in 1838 in unmistakable language—and for the first time—said that cancer is cellular and that the cellular form resembles that of the tissues from which the cancerous growth springs. There in his discovery is the foundation for all modern classification, diagnosis, therapy and research in oncology.

Tonight, using the discovery of Johannes Müller as the dividing point between ancient and modern, I want to outline briefly the conceptions of cancer before and after his work. But mainly I wish to recall to you the man whose discovery we are privileged to celebrate this year.

The external manifestation of neoplasms had, of course, been recognized from early antiquity. The Ebers papyrus gives evidence that the Egyptians knew of tumors, the mention is of a lipoma. Hippocrates wrote of cancers, and used the term carcinas for inflammatory swelling and the term carcinoma for a neoplasm. Celsus went even further; he recognized clearly visceral forms of cancer and attempted to differentiate clinically malignant from benign neoplasms. Galen observed cancers with considerable accuracy but at once obscured good clinical description with theory; cancers came under his doctrine of the four humors. Cancer was due to the concentration of black bile. This humoral theory persisted until after the discovery of the circulation of the blood and of the lymphatics when Malpighi, Louis and Astruc advanced the idea that

cancers were clotted and degenerated lymph. The dominating view to reach the nineteenth century was that cancer was essentially a general disease; that the growth itself was merely a local manifestation analogous in this respect to the pustule in smallpox. Such was the prevailing view until 1838 when Johannes Müller demonstrated that the cancer consisted of an abnormal growth of abnormal cells.

It is true that before Müller, Bichat had made an important step; he had directed the views of pathologists from organs to tissue or, as he called them, "membranes." Morgagni has said that some organ was always the seat of a disease. The fact that identical symptoms might develop when different organs were affected caused some discord in the harmony of this simple view. It was suggested by Pinel—better known for his work in psychiatry than in pathology—that different organs might have similarities in structure and disease in organs with anatomical similarity though in different parts of the body, might account for this confusion. Bichat took up this idea and carried it further with the conception that organs were built up of basic membranes, tissues which were variously distributed in the organs. Bichat made extensive tests in differentiating the tissues even to tasting them but he did not make microscopic studies. He succeeded in removing the seat of disease from the organ as a whole to its tissues. Pathology became at his hands membranous pathology. It was Müller who first made pathology cellular; and the disease he dealt with was cancer.

And now in approaching the man and his work, I ask you to look back with me for a moment at the situation of his native land, Germany, at the opening of the nineteenth century. Müller was born in 1801. The Germany that he faced was socially and economically the Germany of a little more than a century later—the Germany of 1918. It was post-war Germany; a country in the depths of a depression. It was a hungry, sorry, bitter country, bruised and battered. Like a man shocked by too fierce contact with reality it was prepared to withdraw from reality—to turn to philosophy for escape.

The situation as you will recall developed thus: Near the close of the eighteenth century the last political act of Frederick the Great was the establishment of the League of Princes which brought back a semblance of unity to the Old Empire. In France the trends were in the opposite direction; the Revolution was under way. At first the philosophy of reason interested the educated Germans; but the shift to bloodshed and

the overthrow of the government frightened them and alienated them from the cause of liberty. The French emigrés fled to Germany and took up arms there. France protested; Germany soothed and quieted; the French demanded the abolition of the feudal rights of the German Princes in Alsace; again Germany soothed and quieted. Even the fact that Marie Antoinette was the sister of Emperor Leopold did not bring the Germans into war. At most they concluded a defensive alliance with Prussia, and sent a note of protest to France. The French countered with a declaration of war. That was in 1792; the war ended in 1814. It included the rise of Napoleon and his defeat and domination of the German people. It concluded with the battle of Leipzig and the taking of Paris. The war was over—twenty-two years of war and subjugation. Germany was finally victorious but she was left exhausted facing reconstruction.

There was the war generation, and the dead; there was poverty, debt, actual want. In such situations as these there are reactions; and these reactions are wholly unpredictable. In Germany the reaction came as a wave of idealism; a turn from practical, factual views to romanticism, even mysticism. Why centuries before a similar emotional reaction had taken the form of the dancing mania, why in the twentieth century it takes the form we see today; and why in the nineteenth century it was toward romanticism and the worship of beauty—no one can say; the psychology of such national movements is beyond our knowledge for explanation.

This romantic movement was not an affair alone of poets and imaginative writers, of a cult of beauty that revived interest in the medieval architecture and the learning of the East. It was entered into by physicians and naturalists, men whom, in a more rational environment, we should call scientists. The movement was toward what was called in Germany natural philosophy, a quite different use of the term than that applied in England where natural philosophy was natural science. In medicine the movement took the form of speculation, philosophical considerations and especially the attempts to develop systems that in their completeness would give knowledge in totality.

Now we in medicine today have been educated away from this type of thought. Our emphasis today is continually for novelty—for the discovery of the new as discrete bits of knowledge. I suspect that we err in this direction as far as the romantic natural philosophers of 115 years

ago erred in the opposite direction. The weaving of facts into a fabric of order and system is as important as finding the facts but synthesis must come after the facts; so far all extensive attempts have been abortive. We have reacted against this philosophical approach and for good reasons. In the past it has almost invariably led to absurd and untenable systems and to utter disregard of the practical. We have not yet attained enough of the material for synthesis; in the Germany of a century ago it was even more lacking. The fine theories in medicine that aroused the ecstasy of the founders and followers of these fads were not developed in the clinic, the laboratory, or at the bedside. They were spun in armchairs from material as tenuous as the fabric of cobwebs but spun with a pathetically misdirected but feverish enthusiasm. It was an unhealthy state of science—a delirium.

Every fad of medicine, every discovery of science, was made into a system; each system had staunch adherents. Paracelsus was revived and walked again in his followers; the Brunonian system was revered by its disciples; and the philosophy of Schelling permeated everywhere. Mind and matter were identical. Hence the laws of Nature must be capable of direct demonstration in unconsciousness and consciousness in its turn must manifest itself as the laws of Nature. Consequently the laws of nature could be discovered speculatively. This intellectually exalted introspection is, in its subsequent degenerated form, familiar in the works of Mary Baker Eddy and similar writers. But in those days it led in medicine to the development of what Karl Hoffman called his "ideal pathology." Disease was, according to this pathology, a retrogression to a lower grade of evolution. Rickets signified an evolutionary reversion toward the mollusk. Digestive disorders with vomiting had their analogy in the cud chewing of the cow and therefore indicated a regression toward the cattle stage. The one system of healing to persist for any length of time from this phase of German thought was that founded in 1808 by Samuel Hahnemann.

Virtually no sound scientific achievement came from Germany during the first two decades of the nineteenth century. And yet by the fifth decade Germany led the world in medical science—had literally laid the foundation for the type of medicine in which we here were all trained. The man responsible for this change was Johannes Müller. The turning point from natural philosophy (again in the German sense of the word) to natural science came in 1833 when Müller published his Manual of

Human Physiology. It was around him that the great school of Berlin was built—the school that so strongly influenced medical education and practice in America in the late nineteenth and early twentieth centuries. Glance with me at the names of some of the leaders in the medical revival that gave Germany its preeminence: Schwann, Henle, Kollicker, Du Bois-Reymond, Helmholtz, Virchow. Each one of them was a pupil of Müller, trained in his methods, trained to carry on and expand the science he taught. The only great figures of the period who did not spring from his hands were the two clinicians, Schönlein and Wunderlich. It was Johannes Müller who aroused in Germany the enthusiasm for scientific investigation in the basic medical sciences.

Müller was born in Coblenz on July 14, 1801. At that time the French troops occupied the town. His father was a shoemaker but died when the boy was small. His mother was a woman of great energy and with broad ambitions for her family of three boys and two girls. Frau Müller carried on the shoe business with some success; the soldiers who over-ran the place made a market for shoes. Johannes' family were staunch Catholics and the boy's early schooling was with the Jesuits; and it was his family's intention that he should study for the priesthood.

Now some authors who have written of Johannes Müller make much of his early education in its influence upon his later capabilities. In fact, his training has been used as an example of the need for a broader cultural education for modern pre-medical students—a feature upon which I shall comment more fully in a moment. Johannes as a youth received first a thorough grounding in Greek and Latin. It is said, probably with truth, although I find it said with almost monotonous regularity about the youth of famous scholars, that as a child he wrote Latin better than he did German and he found his recreation in making his own translations of Plato and Aristotle. He did remarkably well in mathematics; developed a hobby of collecting objects of natural history, except insects, toward which he had an aversion; and finally, he studied deeply in the humanities; he was a poet of some passing ability, an admirer of Shakespeare and Dante. In short, he had what today—except for the mathematics—we should call a typically cultural education. This fact, as I have said, has been used to impress a necessity for cultural studies in pre-medical education.

Thus Brücke went so far as to say that really worthwhile contributions to science have not come so much from those steeped in science

alone, as from those whose intellectual foundations have been deeper and wider. I do not for a moment doubt this fact, but I do doubt that the conclusions drawn from it can be, as is often attempted, applied to modern pre-medical education. Now it is remarkable but nevertheless a fact that medical educators may interpret matters of science with strict scrutiny and impartial judgment of cause and effect, but sometimes they seem to leave their scientific skepticism behind when they apply their judgment to other fields. With a wholly open mind in the matter I should not be convinced that a humanistic and classical education made Johannes Müller or anyone else a great contributor to medical science. I should wish to be shown that the relation was not wholly one of *post hoc*. Indeed Virchow said that Müller succeeded because he freed himself from the fetters of his early education. One may occasionally wish that the pre-medical education of today might have more science and the medical education less science and more art.

The basic element in the success of Müller is, I suspect, a tremendous intellectual endowment which allowed him to acquire the classics with ease, to read Latin at seven and Greek at ten and not the reading of Latin and Greek at seven and ten that makes his great intellect. We have few Johannes Müllers entering medical school today and there is always danger in attempts at emulation unless the emulator has the intellectual capacity of the man whose educational system he attempts to emulate. The physicians of the time of Molière were highly educated in the classics and in the humanities but that advantage, if it were an advantage, did not compensate for, rather it exaggerated, the deficiencies of a poor medical education. In this digression I merely stated my skepticism as to whether the classical and humanistic education of Johannes Müller was a determining influence toward his later medical productivity. There were many other physicians in Germany educated as well as he was and they did not reform German medicine; they merely devoted their efforts and their education toward the development of humanistically tenable but wholly unscientific systems. I believe that Johannes Müller was a man of superlative intellect and of a personality especially suited to the line of his career. And finally, I think he had opportunity and also some of that nebulous element called luck. Johannes Müller did not spring from the classics fully armed with the medical genius he displayed in later years. He had, as you will see, his difficulties to overcome and his adjustments to make and he did not always make them easily.

He was, as I have said, destined for the priesthood, but at about the age of sixteen he read with great enthusiasm the scientific writings of Goethe. The suggestion there was away from abstract thought and toward concrete factual nature; it was away from natural philosophy in which he had been steeped and toward the natural science of which he then knew so little. I have said that opportunity as well as intellect and personality are necessary for the display of greatness. Without Goethe's influence, Germany might have had a good priest in Johannes Müller and medicine might have lost one.

But whatever the forces were that changed the channel of his career we find him, at the age of eighteen, enrolled as a medical student at Bonn. There he was exposed to two great but opposing forces; one was the philosophy of Schelling toward which he was drawn both by his early education and by a strain of mysticism deep in his own make-up. It was this indefinable spiritual quality which I call here a strain of mysticism that perhaps later inspired his pupils and bound them to him as Virchow says in close ties as if by a religious bond. The other influence, the opposing force that drew him away from philosophy, from theorization and dreamy speculation was, strange to say, anatomy. Anatomy was a factual, realistic subject, the very antithesis of natural philosophy. In the struggle between these two forces, anatomy won out; it aroused his youthful naiveté to the extravagant exclamation that indicates his capitulation: "What does not come under the knife counts for nothing!" It was the extension of this view into the medical education of the nineteenth and early twentieth centuries in this country that made so painful for most of us here the first year of medical school.

Müller in his fourth year of medical education—1823—wrote a prize essay on the respiration of the fetus. Later Virchow, commenting on it, says that it was a work remarkable for the extent of the knowledge shown and for the ingenuity of the experiments carried out.

Having obtained his degree at Bonn, he went to Berlin to take his state examinations and there met, and for a short time worked with the physiologist, Rudolphi. Rudolphi held natural philosophy in contempt; he struck a responsive note in young Müller with his statement that anatomy was the foundation of medicine. Johannes, then twenty-two, was deeply influenced by the skepticism, the worldliness of this older man, and Rudolphi in turn, recognizing the merits of the youth—recognizing too, and perhaps pleased at his own influence upon the keen if still

naive mind, gave the boy an English microscope. The microscope was to play a determining factor in Müller's subsequent career.

The need to earn a living took young Dr. Müller back to Bonn where he made a rather meager livelihood from teaching and from a small practice; occasionally he was assisted by his mother. The death from peritonitis of a friend under his medical care convinced him that the practice of medicine was not to his liking; he dropped it and spent his time on his studies and teaching. These years, one may judge, were trying ones for Müller, a period of adjustments which he did not make easily. In the midst of it, at the age of twenty-five, he married Anna Zeiler, daughter of a landowner near Bonn.

In a poem which he wrote to her he promised her an immortal name in lieu of more material dowry. And then in the frantic burst of scientific research to gain that immortality, his health gave way. I do not know what his trouble was; a breakdown of a nervous nature his commentators say, and one cannot help but assume that these were days of frustration and perhaps unhappiness for a brilliant intellect, a driving ambition—a man torn between mysticism and the study of anatomy, newly married, poor, discontented with medical practice and without the scientific recognition he craved. And all this, be it noted, in an environment where the premium for intellectual endeavor was put on speculative flight of fancy. He did not break seriously under the strain; his health recovered and he returned to his researches. It was in this period that he did his work on the embryology of the generative system remembered in the duct of Müller; it was then also that he carried out his investigations on the nervous system and the sense organs and published his comparative physiology of vision. In that book he confirmed and established Bell's doctrine of spinal nerve fibers. All this and more were completed before he was thirty-two years old.

It was then that Rudolphi died and Müller was called to take his place in the chair of anatomy, physiology, and pathology at Berlin. The following year Müller published the first volume of his Manual of Human Physiology which was, as I have said, to exercise a determining influence in turning the German medical mind away from natural philosophy and toward science. It was to bring brilliant pupils to Müller's laboratory at Berlin.

It is of Müller as a pathologist that I speak particularly tonight. And in that field his important contribution to his students was his insistence

upon the use of the microscope in pathological study. This was a procedure virtually new in pathology and certainly unique as a routine. It was method that he urged upon his students, method of approaching problems and method of solving problems. Those methods must have become almost a primary way of thinking in the men who passed through his hands. They thought in the manner of quantitative evaluations sometimes in little matters as well as large. Thus when DuBois-Reymond wished to tell of the industry of his teacher, what was more natural than that he should use not adjectives but figures. He computed Müller's average literary output for thirty-seven years as amounting to thirty-five printed pages and 0.83 published plates drawn by his own hand each seven weeks.

I have mentioned the names of some of the more important students who were drawn to Müller and inspired by him. Best known of course was the aggressive Virchow, but for the discovery of Müller with which I deal tonight the most important was Theodore Schwann. It was Müller's insistence upon the use of the microscope that led Schwann in Müller's laboratory to discover the animal cell and postulate the cellular theory of tissue structure. It was this discovery which was not published in full by Schwann until 1839 that opened the way for Müller's discovery that cancerous growths were cellular; it also laid out the careers for two of Müller's most promising pupils: Henle, the histologist and anatomist, and, of course, Virchow.

So basic is Schwann's postulation to Müller's discovery that I digress for a moment to trace the outline of its development.

The original conception of a cellular structure is entirely from the botanists. In the seventeenth century Robert Hooke, using a magnifying glass, had noticed the "small boxes or bladders of air in cork." A more detailed structure of plant cells could not be investigated until the compound microscope was developed. It was 1833, the same year that Müller went to Berlin, that the botanist Robert Brown discovered the nucleus in the plant cell. In 1836 (although published in 1838) Schleiden proved that plant tissue is made up of cells and developed only from the multiplication of cells. Müller's amiable and phlegmatic pupil Schwann had seen nucleated cells in animal tissue. Influenced by Schleiden's work he searched for cells in all the tissues he knew of. He found them and from his findings formulated the basic law of morphology for all vegetable and animal tissue. To quote his words: "There is one universal principle of

development for the elementary parts of organisms, however different and that principle is the formation of the cells."

One can almost sense the excitement that must have pervaded the laboratory of Johannes Müller in those years of 1836, 1837 and 1838. Remember that this was before Virchow came there as a student; he was to make the greatest advances with cellular pathology and to obtain the greatest recognition but the fundamental discoveries were made before he came to the laboratory in 1839.

I have already read from the works of Müller how he was led to turn his microscope on cancerous growths and to see the cancer cell and see further that it took the general shape of the cells of tissue from which it sprang.

For my purposes here this basic discovery made public in the year 1838 is as far as I wish to go with the work of Müller. He died, as you know, at the age of fifty-seven, probably of an arteriosclerotic accident, for he was found dead in the bed to which he had retired in good health.

There is just one more quotation from Müller that I make before I leave him. Müller was not infallible but he was sometimes dogmatic. Thus on one occasion he said that the rate of transmission of the impulse in the nerve fiber would never be measured; within a decade his pupil Helmholtz had measured the rate. And again—and this is the quotation pertinent here—when he had finished his work on the histological classification of cancers he wrote in his book these words:

"Microscope and chemical analysis can never become a means of surgical diagnosis for malignant growths; it were ridiculous to desire it, or to suppose it practicable."

Now if there is any one thing in which microscopic examination of neoplasms has been useful, practicable, it is diagnosis.

The enormous volumes of microscopic anatomy of neoplasms are at once a refutation and also a little justification of Müller's dogmatization. The morphological studies for classification go on endlessly with a descriptive refinement that forces one to the conclusion that while the microscope shows the cancer cell, this cell itself has no fixed morphology, only approximate. If one may hazard here a dogmatization with all dangers of dogmatization it is that cancer morphology has not and will not contribute toward the really fundamental discovery sought today—the reason for the cancer cell—cancer causation. The search today still centers on the cell but not its shape, rather its physiology, not cellular

morphology, but cellular reaction.

Johannes Müller's statement that cancer is cellular has remained since his day the foundation of all cancer research. Literally everything we know about cancer, except its gross appearance, has been gained in the single century that has passed since his publication of 1838.

Cancer causation was from the beginning and is today the great riddle. And such knowledge as we have gained and are gaining makes each year more dubious the possibility of any completely successful method of treating the developed cancer. I do not mean in any way to belittle the achievements of the therapeutists or to imply that the wider and fuller application of their measures would not save many lives. It would. But everyone in medicine knows that the often quoted slogan of early detection and cure has elements of well intended sophistry. They know, too, that no new successful principle of treatment has been developed since the time of Hippocrates. In his day there were surgery and caustic plasters; in our day there is better surgery while radium and x-ray have replaced the caustic. The aim then was, and the aim now is, to remove or destroy the neoplasm. The principle is unchanged. We all see, I think, that success must lie in other directions. And the essential to that success must be the discovery of cancer causation. Occasionally specific therapy is discovered accidentally before the cause of the disease is known. But such is rare. Usually the discovery of the cause must precede the development of treatment or prevention.

The scientists of Müller's day saw that fact and they gave us hypothesis; there was Virchow's chronic irritation theory, Cohnheim's stimulation of misplaced embryonic rests with Ribbert's later modification; there was the heredity and there was the parasitic theory.

The experimental scientific investigations that have given promise of the eventual solution of cancer causation showed first the autonomy of the cancer cell. Hanau, as early as 1889, made successful transplants of cancer cells in rats; his work was confirmed in 1901 by Loeb and in 1903 by Jensen. It was carried to its logical conclusion by the *in vitro* growth of cancer cells by the method of Harrison.

Next in these few and broad steps I take in reviewing cancer study was the experimental production of cancer. This new era in cancer research started with Fibiger's discovery of the cancer in the stomach of the rat caused by a nematode carried by the cockroach—in itself one of the most exciting stories in modern scientific research. Fibiger's work

stimulated interest and efforts to produce experimental cancers and next came the tar cancers in the ears of rabbits.

It is a long jump from there to the discovery in tar of the carcinogenic penathrene ring; and the discovery of this ring in normal secretions of the body and in vitamins. It is a long jump too from simple tar cancer to the virus cancer of Rous and still another to the isolation of at least one virus as a non-living chemical substance. Today cancer research moves from the microscope to the test tube; from morphology to chemistry. And the promise held today for the discovery of cancer causation and for the subsequent relief from the scourge of cancer grows brighter.

The great danger to the search for the solution of the cancer problem is not ignorance; not lack of means of approach; not failure of science; it threatens always from another direction. It is the danger that some social cataclysm shall shake the rock of science and dislodge the scientist. It is then that men's minds lose the desire for facts, for realities; they turn to the consolation of philosophies, they turn to bizarre social manifestations. This has happened in the past; it may well happen again. Science, as we know it, is a solid structure but the scientist who builds upon it is a man and as a man is at the mercy of his social environment. That is the frail structure and the scientist is no stronger than its strength. German thought of a century ago rose as I have traced from speculation to productive science; within our time it fell again. These things are not of one country, or of one race, or of one century. They are universal and eternal. And so I say again, barring the social cataclysm that will dislodge the scientist, the way is clear and open to the discovery of cancer causation.

Perhaps in this building or its successor a hundred years from tonight there may be again, with the problem of cancer then solved, the suggestion that the memory of Johannes Müller, who defined the problem for its solution, be revered. You and I will not be here. But I hope that he who is privileged to recall the memory of that occasion will recall the man as he is recalled in the words of his pupil Virchow. They are almost a prayer in the rise of science above social retardation. He said:

"The cult which he served as a priest of nature bound his pupils to him in close ties, as if by a religious bond; and the serious priestly fashion of his speech and movements compelled the veneration with which everyone regarded him. His mouth, with its tightly compressed lips, conveyed a notion of severity; around eyes and forehead played an expres-

sion of profound thought; every furrow in his face stimulated the idea of a perfectly finished work—thus did the man stand before the altar of nature, freed by his own energies from the fetters of education and traditions, a living witness to personal independence!"

EMOTIONAL FACTORS IN HYPERTENSION*

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As I consider the elaborate and thorough-going discussion of renal medicine which has been prepared by your committee for this Graduate Fortnight, I am appalled at the responsibility which devolves upon me as almost the lone contributor to a consideration of the psychological factors in disease. That this aspect of the symptom of hypertension or of the diseases in which it occurs should have been included on the program, even this once, may be taken as an indication of the change in medical attitude since those days when a reference to psychology was tantamount to a reference to spiritualism or necromancy. If, on the other hand, one brief hour out of hundreds devoted to this point of view seems disproportionately small, it may be charged in part to a lingering reluctance to consider psychology a definite science, and, in part, to the far greater precision of the microscope and the test tube as compared to our measurements and estimates of human behavior and emotion.

Since I have so large a subject to present in so short a time I cannot now analyze further our resistances to psychological concepts in medicine or refute the impression that the scientific method cannot be and has not been applied in psychology as in physiology and chemistry. I shall indicate first the point of view which I think probably correlates the psychological, physical, and chemical findings in disease; then I shall present some of the psychological data which have been accumulated concerning the subject of hypertension, abbreviating the physical and chemical aspects which have been so excellently presented in previous lectures here; I shall indicate some of the practical difficulties in arriving at more definite and exact conclusions than we can offer at the present time, and, finally, I shall submit a few practical suggestions.

Point of View: I truly believe that the word *psychogenic* has done more to confuse the issue of the emotional factors in disease than to clarify it. Psychogenic as applied to an illness implies that the disease arises

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some way or other in the patient's mind and, with the persistent medieval concept of mind which prevails not only in medical thinking but elsewhere, this is equivalent to saying that some diseases are consciously or unconsciously conjured up out of "mind-stuff" and deposited upon a surprised and unwilling body which functions according to physical and chemical laws independent of psychological laws. As one intensely interested in studying the emotional factors in disease, and one who has proposed numerous postulations concerning the contributions of these factors to disease, I should like to make the bald statement that I do not believe that any disease is psychogenic.

Such a one-sided attitude is no better than that held by the clinician who totally ignores the psychological factors in disease and thinks of disease solely in terms of physics and chemistry. For I do not believe, either, that any disease can be accurately described as physiogenic or chemogenic. Physics overlaps chemistry and both overlap psychology, but the laws of one are not the laws of the other in our present state of knowledge. The time may come when we may describe in a single mathematical language a stone in the kidney, an antitoxin in the blood stream, and the reactions of a child who sees his mother strangled. But at the present time we scientists must profit by the example of Aesop's six blind men and the passing elephant. We must each lay our hands upon it from the vantage point that is ours and, by comparing results and trying out hypotheses to explain the discrepancies in our observations, instead of contradicting and ignoring one another's data, we may avoid the ignominious errors of the six blind philosophers.

My feeling is that as a result of traditional medical education, most patients are examined physically and chemically but not psychologically. We would call a man a quack who treated a case of appendicitis after making a psychological examination but no physical examination; why should we condone the treatment of a case of anxiety hysteria after a physical, but no psychological examination? If we truly subscribe to the theory that in every disease the proper investigation would uncover psychological as well as physical and chemical features, we must believe in the existence of a special psychology for every disease. Perhaps the medical textbook of the future will systematically supply these. For the present we must content ourselves with a much better knowledge of the psychology of certain kinds of indigestion, for example, and even of gastric ulcer, than of the psychology of chronic nephritis or carcinoma.

And now for the psychology of hypertension:

Hypertension is, of course, not a disease but a physical condition which is easily ascertainable and measurable. Parenthetically, I have often wondered if the introduction of the sphygmomanometer has not killed more patients than it has saved. In our search for definiteness in biological science, it is difficult to remember that precision in measurement is not equivalent to accuracy in interpretation. The feeling of security which followed the introduction of this ingenious device of Riva-Roci and von Basch led us astray and numbers became more important than meaning. Many a doctor has frightened his patients to bed if not to death with an ominous and incorrect interpretation of the incontrovertible figures of the dial or mercury column.

But hypertension is a condition in which not only the physical but also the psychological factors are readily recognizable, although the latter are not so easily measurable. The parallelism of blood pressure fluctuations and emotional fluctuations was one of the early physiological correlations.*

Of course we have learned a good deal about blood pressure since those earlier days.** We—or some of us—have ceased to look so assiduously for a "cause" of hypertension and have sought rather to understand its total significance. From the physiological and anatomical standpoint, we are quite generally agreed that it is due to vasoconstriction and that the vasoconstriction is due to sympathetic stimulation and parasympathetic inhibition. That these effects accompany or are accompanied by emotion is also generally accepted.

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* "The influence of the theories which embodied the organic explanation for the increase in peripheral resistance in primary hypertension has not as yet been erased. For this, the term hypertension itself is largely to blame in that it implies a static phenomenon. The lability of the blood pressure, first recognized by Gumprecht[1], emphasized by Mosenthal and Short[2], and reiterated by Ayman[3], is the most singular characteristic of essential hypertension and is not sufficiently appreciated. These striking fluctuations of the blood pressure imply a morbid physiology, only the sequelae of which can be anatomical. In the opinion of Kylin[4] this lability of the blood pressure is explainable only on the basis of a vasomotor disturbance, which is in accord with the view of Norris and his associates[5], who state that the vasomotor mechanism in patients with essential hypertension is sensitized and that hypertension in those instances is simply an exaggeration of a normal physiological blood pressure response. These contentions are substantiated by the findings of Mueller and Brown[6], that the diurnal and nocturnal fluctuations in blood pressure in normal individuals and in patients with essential hypertension differ only in degree, and that patients with essential hypertension show extreme reactions to stimuli which in normal persons would cause only mild reactions. That is to say, the blood pressure responses to emotional stimulation in the hypertensive and in the normal individual are qualitatively the same, the difference being only from a quantitative standpoint. That the ordinary and usual incidents of life provide stimuli sufficient to cause marked fluctuations in the blood pressures of patients with essential hypertension has been demonstrated by Brown[7], O'Hare[8], and Mosenthal and Short[2]."

** To the older writers, of course, hypertension was primarily a disease of the blood vessels of the kidneys which in some toxic or mechanical way affected the rest of the vascular tree; when this theory was exploded by further clinical studies the blame was put upon the suprarenals. Later guanidine, cholesterol, peptone-like substances, the potassium-calcium ratio, to say nothing of alcohol, tobacco, hypoactivity of the carotid sinus and numerous other agents were inculpated, one after another of which has been disproved as the fundamental etiologic basis of arteriolar hypertension.[9]

Whether the emotion is a cause or an effect of the hypertension still seems to puzzle many writers. On the one hand, many physiochemical researches proceed as if the emotional reactions were by-products. On the other, many practical procedures such as the lie detector* proceed upon the assumption that emotional disturbances can cause blood pressure fluctuations.

At this point may I refer again to the elephant and the six blind men. I see no reason why we should feel it necessary to seek for first causes when our daily experience, if not logic and philosophy, convince us that none such exists! What impresses some physicians who palpate the elephant is the fact that they find certain definite, characteristic, structural and chemical pathology in advanced and fatal cases of hypertension. What impresses those who have made psychological examinations of the same elephant is three-fold:

(1) The fact that transient hypertension may be induced in persons by emotional stimulation.

(2) The fact that some of these cases show gross abnormality of emotional status or reactions.

(3) The fact that chronic hypertension may sometimes be reduced by various procedures essentially psychological in nature.

Without attempting to solve the riddle, which may be, after all, like the riddle of the priority of the chicken or the egg, I propose to devote my remaining time to an examination of these three sources of psychological data.

1. Transient Hypertension in Normal Persons

I have already discussed this briefly. The only point I would add here is an echo of what is now becoming increasingly familiar to all investigators; namely, that we do not know very definitely what a normal blood pressure curve looks like, since single readings are almost meaningless and continuous readings almost impossible to obtain. Hence hypertension is a relative term of great inexactness. I have seen the systolic blood pressure of a patient who was being examined by an assistant mount

* The theory upon which the deception test is based was suggested as far back as 1600. Hugo Muensterberg of Harvard suggested the use of an instrument for recording blood pressure, pulse and respiration for the detection of guilt in 1907, and Marston in 1914 experimented with a blood pressure technique for detecting deception. Larson[10, 11, 12] continued the work under direction of Chief of Police August Vollmer in Berkeley, California, and succeeded in establishing a successful technique. Keeler[13] designed an instrument for recording simultaneously the blood pressure and respiration over a period of time which is widely used today. (See also Inbau[14]).

fifty millimeters of mercury merely as a result of my entrance into the room. We have no way of knowing how much it may have mounted previous thereto as a result of my assistant entering the room, or as a result of applying the cuff. The practical utility of the lie detector has been proved, but what we do not know is how much the anticipation of applying the lie detector may have affected the arterial tension in the first place. Of course this does not invalidate the test. I simply mention it to show that until we are able to take a patient's blood pressure without his knowing that we are taking it, we have no way of knowing what it *was*. We do know[15] that the blood pressure of a person with what we call normal vasomotor stability usually rises with certain emotional states, which may be experimentally stimulated, and returns rather promptly to a lower point. To explain a systematic elevation of blood pressure it would be necessary to assume a continuous series of such stimuli. This, of course, is one deductive theory offered to explain the relation of the emotional pathology found in actual cases of hypertension to that hypertension. We shall look next at some of these cases in which this continuous or chronic emotional pathology has been found.

2. Emotional Pathology in Hypertension

We psychiatrists sometimes reproach internists for their apparent disinclination to seek for the psychological data which might be related to the continuous autonomic stimulation which results in the continuous splanchnic constrictions which result in the hypertension. I want to withdraw all my reproaches, because I can testify from personal experience that collecting data regarding the emotional factors in hypertension is for many reasons an exceedingly difficult task.

For one thing, one must distinguish between conscious and unconscious emotional factors. It is hard enough to uncover the conscious emotional pathology of a patient and to evaluate its strength, its effect upon his total personality and his vascular tension, in particular. It can be done, usually, if one has the patience to listen to what the patient has to say. But it is still harder to get at the unconscious emotional factors, those which the patient cannot tell us about even if he would. This requires the psychoanalytic technique, and, therefore, a great amount of time.

It is very hard, too, to separate the emotional factors stimulated by the physician himself and by the whole program of examination and

treatment from those more continuously operative. Again, even when one discovers and evaluates the emotional factors in a particular case quite definitely, it is exceedingly difficult to show except by deductive hypothesis just how or how much these things affect the blood pressure. It is impossibly absurd, for example, for a psychoanalyst who is listening quietly to a patient who, with sobs and tears, is confessing some poignant source of anxiety, to interrupt this by leaping from his chair to seize and apply a sphygmomanometer. Or consider this complication: I was conversing with a patient with very severe hypertension while an assistant took blood pressure readings regularly every two minutes. The patient had voluntarily renounced smoking after many years of heavy addiction. I proposed that we observe the effects of smoking a cigarette and he willingly cooperated. My assistant redoubled his efforts to make accurate consecutive readings. While we were waiting for the cigarette "to take effect", my patient suddenly remembered a distressing occurrence which had taken place in his home the previous week and began to relate it in detail. His systolic blood pressure rose thirty millimeters of mercury but whether from the cigarette or from the recollection, who can say?

Nevertheless, in spite of all these difficulties some definite psychological studies have been made both of the conscious and of the unconscious emotional factors in hypertension and some fairly definite tentative conclusions arrived at. In the brief time at my disposal I can only summarize these conclusions.* Wolfe[16], Dunbar[17,18], Hill[19], Stevens[20], Alexander[21], Moschcowitz[22] and others have reported such studies. The findings correspond fairly well. They indicate that patients with hypertension are characterized by an external poise, often gentleness and amiability, be-

* For example, Wolfe[16] studied hypertension cases in the medical department of the Columbia Medical Center. He believes that the development of hypertension is the result of repressed (i.e., unconscious) emotional factors, chiefly aggressions, hatred and guilt feelings.

"To what extent this situation is specific we are not ready to say. It seems noteworthy, however, that successful handling of this factor alone . . . surprisingly often leads to improvement or even symptomatic cure, although the fundamental neurosis may not have been adequately treated." He cites a case of a single man of 25 admitted to the hospital for hypertension, his blood pressure being in the neighborhood of 160/90. He also had some fears of fainting and was found also to have deep but largely repressed resentment and hate. His dreams, for example, were of a predominantly sadistic-masochistic character. After three months of superficial psychotherapeutic treatment emphasizing relaxation, his blood pressure was reduced to 136/88.

Dunbar[18], working in the same clinic, reports among others a case of hypertension in a married woman of 39. Her blood pressure on admission was 190/100 and was said to have been higher previously. A careful psychiatric study showed that there was much reason for the existence of great resentment, anxiety and hostility and when these tendencies were to some degree brought to consciousness and related to her symptoms, she showed a marked improvement in her external adjustments and coincidentally a drop in her blood pressure to an average of 130/90. This was accomplished in a few months, which is rather extraordinary in view of the fact that she had been an invalid on account of such symptoms for the preceding eighteen years.

neath which there exists a strong undercurrent of fear which arises from the existence of strongly repressed aggressions, usually dependent upon resentment over threats to the patient's dependent security. To re-phrase this rather condensed statement by a paradigm, I would say that hypertension might be expected in a patient whose early childhood was threatened by poverty, death or other disaster whereby he was forced into a premature self-reliance which later shows itself in the form of more or less external (material) success, but accompanied by a constant internal anxiety set up by actual or imagined threats to his security. Upon examination such patients completely deny or reject all suspicion of resentment, hate or fear but describe situations in which such emotions could not but be stimulated. Continued study of such patients often evokes, suddenly and sometimes to the patient's great surprise, frank avowal of such feelings, and then, the real (i.e., the original) reasons for them.

I remember, for example, a dramatic experience with a patient, an author, who came to us because of the sudden loss, two years previously, of her ability to write. It was discovered incidentally that her systolic blood pressure readings were continuously over 200 mm. of mercury. After a few introductory sessions in my office during which she was pleasantly, but irrelevantly, communicative; she suddenly asked for paper and pencil, ceased talking and began writing automatically. The handwriting was not her own and the communications were signed by a strange name. She had never done this before. She dashed off hundreds of pages in this way during the next few weeks. She was amazed at what she wrote since it concerned herself, intimately, and while she was able to confirm its truth after she had written it, she insisted that she had known nothing about it prior to the automatic writing. Among other things she confessed frank wishes to kill her mother for reasons, also given, which seemed at least partially to justify such wishes. She ultimately regained her ability to write professionally and her hypertension diminished.

A more characteristic example is that of an old maid who for thirty years had been the trusted private secretary of the executive head of a large business. Apparently he had supreme confidence in her and was absent from his office weeks and even months at a time. Much as she appreciated this confidence, however, and great as her admiration and respect for her employer were, she was exceedingly distressed by the growing rebellion of factions in the business which threatened to over-

throw his control of it, and, incidentally, remove her from her position. When she would appeal to him to return and assume the responsibility of controlling the business, he would reply that he had confidence that she would do the right thing. This she felt totally unequal to, but never one word of criticism or reproach of her employer would pass her lips even in the intimacies of a professional consultation. This depression and psychic tension were associated with a high degree of arterial hypertension.

In this connection it may be fitting to say that in several cases in which I have made blood pressure readings in connection with psychoanalytic treatment I have observed a temporary increase in blood pressure for several months toward the end of the analysis, corresponding with the resentment and fear experienced by the patient over the contemplation of being extruded from the protective care (as he envisages it) of the physician. Of course an analysis is incomplete if this fear and concomitant hypertension have not receded as the patient takes a more realistic view of the situation and increasingly utilizes his capacity for directing his hostilities into useful channels, thereby also reducing his feeling of helplessness.

The objection may be made that cases of hypertension studied by psychiatrists are exceptional in nature and hence not suitable material from which to draw general conclusions about hypertension. Without conceding this to be a valid objection, I personally undertook, as have some other psychiatrists[16,17], to make psychological studies of patients, referred, by cooperating internists, for this purpose only. My purpose was to see if a week's intensive study would lead to any inferences as to the *probable* nature of the unconscious material, and to any practical conclusions as to the significance or potency of the conscious emotional factors. I had in mind the opportunities and necessities of the average general practitioner or internist to whom we psychiatrists are constantly commending the desirability of searching for and dealing with the emotional factor in disease. What could a doctor who was trying to do this see in carefully studied cases of hypertension, and what further could one with psychoanalytic experience justifiably infer or suspect?

An illustrative case can be mentioned briefly. A married woman of fifty-one, with a blood pressure averaging 183/104 and occasionally much higher, had a fairly characteristic psychological picture. She was an exceedingly gracious and dignified, composed person, amiable at all times

under the varied experiences of a complete psychiatric examination. For ten years she had been the executive head of a large international organization and had traveled extensively in Europe, Asia and all parts of this country making addresses at large and small meetings. She was married to a physician twenty years her senior. Two years prior to the discovery of her hypertension he had been removed from a position which he had held for many years and was attempting to make a living for his wife and himself by the re-establishment of a private practice. Progressive loss of vision made this still more difficult. The frequent public appearances which his wife was obliged to make in connection with her work required an expenditure for clothes at a time when it was even difficult to buy sufficient food. This financial restriction in conjunction with her pride and the necessity for making a good appearance before her townspeople and her organization was an increasing source of conscious anxiety to her as was also the increasing age and anticipated helplessness of her husband. As she was discussing this latter point her systolic blood pressure mounted to 238 millimeters. Consciously, of course, it would have been absurd for her to blame her husband for their predicament but the unconscious is not guided by any such rules of justice or fair-mindedness. Hence her hostility was repressed; the inner psychological tension paralleled the high arterial tension.

3. Therapeutic Effect of Psychological Techniques in Hypertension

In referring to the work of various authorities with hypertension cases, I have not mentioned the frequent reports of cases benefited by psychotherapy, the third fact which impresses the psychologically minded observer. Some of these are very striking; Hill[19], for example, reported a case of a man of thirty-two who for fourteen years had been known to have hypertension. This patient was under treatment by psychoanalysis and following one particular day's treatment, the details of which have been completely reported by Hill, his blood pressure fell from an average of 180/120 to 145/90 and thereafter never exceeded 135/90 and was frequently read as low as 125/85. No other treatment was administered and there was no change in his habits of living. I myself have reported a few cases[23] and I have already referred to the fact that frequently patients show a rise and then a fall in blood pressure near the termination of an

analysis. This observation has been confirmed by an ingenious piece of clinical research reported by an internist, David Ayman[24] of Boston. Ayman was impressed by the widely varying reports of the successful treatment of essential hypertension by many different drugs and methods. He carefully analyzed thirty-five research projects of this type and discovered that in practically every article complete or partial symptomatic relief was reported in spite of the enormous range of treatment methods. He noted, also, that complete failure was seldom reported. He concluded that there must be some common factor associated with the administration of these various treatments which was not recognized by the experimenters, and as a research project studied the effect of the administration of a placebo (dilute hydrochloric acid). As minimal criteria of a diagnosis of essential hypertension he insisted that the patient should have had at least five abnormally high readings of blood pressure and that they should have been observed for at least two months prior to the beginning of treatment. An otherwise unselected group of forty patients was then treated and followed. Thirty-three of the forty patients showed definite improvement, i.e., the treatment was 82 per cent successful. The symptoms were relieved and the blood pressure fell, however, with a considerable disparity in the parallelism of the two factors.

Ayman was convinced that the common element in the treatment to which the patients responded with so much benefit was that of "the enthusiastic giving or doing something for the patient." His point is that *treatment*, regardless of its nature, benefits the hypertensive patient. Not being a psychoanalyst or psychiatrist, he does not interpret this in terms of the transference effect with which we are so familiar, but makes it clear that the patient feels better because he is now under the protective observation of an individual of authority who takes an interest in him.

How closely this corresponds to the psychoanalytic findings already reported scarcely needs elaboration. If even the placebo of dilute hydrochloric acid used by Ayman is sufficient to give 82 per cent of success in treatment of the symptoms with an unrecorded percentage of success in the reduction of the blood pressure itself, one must assume that some emotional experience takes place which lessens the symptoms and the tension and presumably this is brought about by a lessening of some inner

tension which the patient unconsciously maintains.*

These are the aspects of the elephant that impress the psychologically minded. How they are to be correlated ultimately with the physical and chemical findings, I do not know. There is a theory that would adequately reconcile some of the discrepancies in our viewpoints. Let us think of the physical observations in regard to hypertension as one aspect of the disease and let us think of the chemical observations that have been made regarding it as another aspect and let us think of the psychological observations as still another aspect. Let us refrain from assuming that any one of these is responsible for the others. In other words, let us not attempt to explain the irritability of the hypertension patient as *due to* his tension, and let us not explain the hypertension as *due to* guanidine or disturbance of the potassium-calcium ratio or anything of this kind; let us not explain the kidney changes as *due to* the arteriosclerosis or vice versa. In these fields let the descriptions stand by themselves and let us look for something back of all of these observations which may be regarded as a coordinating determinant. This, I think, is the value of the concept of *primary constructive and destructive tendencies* with which we are familiar in metabolism, the phenomenon of inflammation, the chemical process of ionization and similarly in the field of behavior. Lack of knowledge precludes our finding very apt words to describe it and perhaps Freud's choice of the expressions "life instinct" and "death instinct" was not the most fortunate one. But certainly the idea of two opposed but interacting forces, one in the direction of life and creativeness, and one in the direction of death and destruction, manifesting themselves in physical, chemical and psychological phenomena, lends itself in a very fruitful way to our problem. What we call physiological and chemical and psychological observations are all interrelated mechanisms resulting from instinctive drives originating deep in the structure of the personality.

* We might here examine the thesis set forth by some of the more progressive internists (see Allen[33] *et al*) to the effect that hypertension probably arises upon a "constitutional," i.e., hereditary, basis which is designated as the specific factor, and to which some non-specific factors, toxic, psychic, or mechanical, are added to produce the final result. There is very good evidence for this view, particularly the frequent occurrence of hypertension in certain families, the evidences of predisposition to hypertension in certain individuals who show the vasomotor hypersensitivity indicated by the Hines-Brown Test.[35] On the other hand, *it is well-known that Negroes and Chinese do not in their native countries develop hypertension.* It is also well-known that people of these same races do develop hypertension in the United States or under other circumstances of occidental culture. This fact is rather devastating to the constitutional or specific theory. It is, on the other hand, entirely understandable from the standpoint of the psychogenic theory. This will require some explanation because one's first thought is that certainly the Chinese in China and the Negroes in Africa have plenty of occasion for fear in those countries, perhaps even more so than in this country. But there is one source of fear from which the Chinese and Africans do not suffer under the domain of their native civilization which they do experience in ours and this is the anxiety arising from the strong super-ego development which the occidental civilization induces.

Practical Suggestions

Whether this theory is correct or not, it has at least two pragmatic evidences of validity.

In the first place, it has been definitely demonstrated that a passive conversational approach to a patient often enables the release of some resentment (and hence of the necessity of some repression, and of some fear) and this decrease in psychic tension should be reflected in a decrease of vascular tension. Whether clinicians agree with the explanation or not, there is general agreement in the literature as to the observation and, therefore, as to the therapeutic validity of this method of treatment, a method which, nevertheless, is shockingly neglected. To put it in plain English, physicians may definitely relieve hypertension by giving the patient a quiet, non-critical, sympathetic audience. All reference to the degree of hypertension, its potential dangers, its complications, is omitted from the conversation. The effect is not one of suggestion; it perhaps needs to be said that for such patients encouragement about the reduction of blood pressure is not necessarily good therapy; in his unconscious, each patient needs his symptoms and to encourage him to think that these symptoms are disappearing without a perceptible reason may undo the good done.

Another practical suggestion: There is much reason to believe[26,27] that self-directed aggressions can be turned outward by the authority of the physician and if our theory has validity, any extroversion of the aggressions which is not mechanically too strenuous should be of benefit to the patient. In other words, instead of forbidding exercise to a hypertension patient, it should often be recommended; instead of prohibiting work, it should be insisted upon. I am confident that the death of some hypertensive patients is hastened by physicians who remove from them the only available or acceptable forms of aggression to which they have had access, i.e., golf, walking, or hard work at the office. Many internists know this intuitively and I have heard them cavil at those colleagues who still preserve a childlike faith in the socalled "rest cures." My own clinical experience with hypertension is not sufficient to know how generally correct or incorrect it is but certainly the psychological theory is all on the side of those who advocate *mild** exercise and continued work and regard the forbidding of these things as the greater hazard.

* Of course one can overtax long-weakened vessels.

Conclusions

No one man can see enough patients representing any one syndrome to draw any final conclusions about it. When I consider the millions of patients who exhibit the symptom hypertension and compare those with the paltry few that I myself have observed or even the few thousands that I and all my colleagues together have seen, and examined psychologically, I realize that we must rely upon deductive theory rather than upon inductive positiveness for our working hypothesis. What some of us have observed, who see with psychological eyes, or, to retain my metaphor, who feel with psychological hands, I have tried to set forth briefly. I have even hazarded a theory of reconciliation of the known facts. I shall now listen with the utmost interest to what my colleagues have to say about the physical and chemical aspects of the same condition. Perhaps after many years of continued study and comparing of notes we shall have arrived at a comprehensive view of the condition in which arterial hypertension is one symptom.

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THE TREATMENT OF ACUTE GLOMERULONEPHRITIS IN CHILDREN*

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Two hundred and nineteen cases of Bright's disease have been diagnosed during the past eight years at the Babies Hospital. This number does not include patients with purulent nephritis or chemical poisoning. These patients with Bright's disease were grouped according to the commonly accepted classification as follows:

Acute Glomerulonephritis	144
Acute → Chronic	2
Chronic Glomerulonephritis	29
Nephrosis	46

There is no good reason to attach much importance to these figures since the great majority of patients with acute nephritis are probably not seen by the doctor. In practice and in the clinic we see the child with a severe infection and a mild nephritis disclosed by routine examination or more rarely the child whose nephritis is severe enough to bring him to the clinic or physician. Our figures simply illustrate the general experience in the eastern cities and show that acute glomerulonephritis and nephrosis are childhood diseases; in adult practice these conditions are relatively uncommon. These figures also show how rarely it is possible to observe the transition from acute to chronic nephritis. I have no explanation for the figures of Snoke and Addis who found that 40 per cent of their patients eventually developed chronic nephritis. I don't think that the difference in technique used in urinalysis accounts for the discrepancy. Perhaps the difference is regional. But chronic nephritis is a complicated controversial problem and my subject tonight is a discussion of some factors in the etiology and treatment of acute glomerulonephritis.

There is abundant evidence that acute glomerulonephritis is preceded and accompanied by hemolytic streptococcus infection with great regularity. The most common seat of infection is in the upper respiratory

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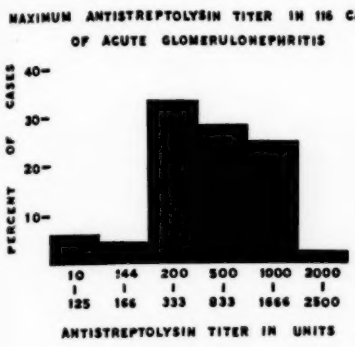

CHART I

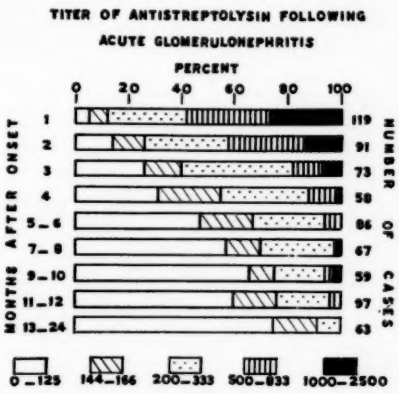

CHART II

tract and adjacent structures. Clinically, we know that the seasonal and geographical incidence of acute nephritis in children parallels that of streptococcus infection. There is no doubt that other organisms can stand in association with typical clinical and anatomical acute nephritis but the number must be small. With Doctor Seegal, Doctor E. N. Loeb and Miss Jost we have studied the antistreptolysin titer of the blood serum in acute nephritis. Chart I shows the maximum antistreptolysin titer of the serum in 116 consecutive cases of acute glomerulonephritis. Ninety-five of these patients are under thirteen years of age, twenty-one are adults. It has been found that in the great majority of normal individuals the antistreptolysin titer is less than 125 units. We think this chart which shows that 9 per cent of patients with acute nephritis have an abnormally high antistreptolysin titer indicates that in New York City the great majority of patients with acute nephritis have had a streptococcus infection preceding the nephritis. In chart II is shown the titer of antistreptolysin in the two years following the onset of acute nephritis. The percentage of normal antistreptolysin titers increases with time until in the second year they are 75 per cent. This period serves as a control for the group. So far as we can tell the variations in antistreptolysin titer are not related in any way to the severity or duration of the acute nephritis but are very closely related to the type and severity and persistence of the streptococcal infection. My object in showing these data is to illustrate the great regularity with which hemolytic streptococcal infection precedes acute nephritis.

The mechanism by which streptococcus infection produces nephritis is not known. It is not by direct bacterial invasion of the kidney. Escherich and Schick suggested as early as 1912 that it "might be a case of hypersensitivity of the organism which is expressed in the ability of small amounts of pathogenic substance to elicit clinical symptoms which at another time would be tolerated without any reaction." They pointed out the analogy between the sequence of events in postscarlatinal nephritis and that in the group of allergic reactions. This is the theory held by most observers today. Masugi and later Farr and Smadel working with nephrotoxic serum have produced a nephritis which clinically and anatomically closely resembles acute and chronic nephritis. However, until the disease is produced by hemolytic streptococcus in the experimental animal many questions must go unanswered.

With this brief discussion on etiology as an introduction I should like to go now to the question of the treatment of children with acute nephritis. Volhard states that in treating acute glomerulonephritis the problem consists in: 1) Preventing the different dangers which may threaten the life of the patient during the acute stage, 2) preventing irreparable organic changes in the kidney. Volhard believes that early diagnosis and proper treatment during the acute stages is an important factor in the prevention of chronic nephritis and goes so far as to say that none of his patients seen and treated in the acute stage develop chronic nephritis. I am unable to convince myself from the evidence available that we can prevent the development of chronic nephritis. However, my experience has led me to believe that early diagnosis and adequate treatment at the proper time may prevent some of the fatalities in the acute stage of the disease.

Table I shows the mortality in acute nephritis in children as reported by different observers.

TABLE I

MORTALITY IN ACUTE NEPHRITIS IN CHILDREN

Cause of Death	*Number*
Infection	28
Cerebral Edema	9
Renal Failure	12
Uremia (type not stated)	13
Cardiac Failure	6
Total Deaths	68 (9.4%)
Total Number of Cases	722

It is seen that forty of sixty-eight deaths were due to cerebral edema, cardiac failure, uremia and renal failure and twenty-eight deaths were due to infection. It is a difficult matter to be certain of the cause of death in acute nephritis. In our own series where death was ascribed to cerebral edema, cardiac or renal failure, infection was an important contributing factor. Clinical experience leads one to believe that in any death from acute nephritis all four conditions may be present in some degree.

The conception that acute glomerulonephritis is but one manifestation of widespread capillary injury is rapidly gaining ground. We have not time to examine the history of this theory or the evidence for its support. The experimental results are conflicting, and much of the evidence is indirect. The physiological mechanisms are not known, but it seems probable that capillary constriction generally, as well as in the glomerular tuft, is an important feature. Baehr contends that unless extrarenal manifestations (edema, hypertension) are present the case is not true acute glomerulonephritis. And he would have us believe that all the glomeruli are involved in the process. From what we do know of etiology and pathogenesis and from anatomical studies in children it seems to me unreasonable to so limit the diagnosis of acute glomerulonephritis. It is known that this disease is an acute often explosive process and that the extrarenal manifestations may occur and not be observed because the patient does not come to the clinic until they have passed. It is also well known that glomeruli do not function continuously and it is reasonable to assume that some of them may escape injury by the hypothetical circulating toxins. This is proven by the work of Oberling who found from a study of biopsy material that the damage was focal and not diffuse. We are concerned here with the fact that clinical manifestations of this generalized capillary involvement are seen in over half of the cases if they are carefully looked for, and in approximately 10 per cent of the cases cerebral and cardiac symptoms and renal shut-down are severe enough to warrant serious therapeutic consideration.

The symptoms and signs which point to cerebral participation in the arteriolar spasm are easily recognized and are present in some degree in over half the children with acute glomerulonephritis. Oliguria, a rising blood pressure, symptoms of increased intracranial pressure, such as nausea and vomiting, headache, somnolence, visual disturbances, slow respiration, and slow pulse are prodromal signs of cerebral edema. There may be an increase in peripheral edema, papilledema and nitrogen reten-

tion may or may not be present, and lumbar puncture may show increased intracranial pressure. When the condition becomes severe, coma, delirium, amaurosis, and convulsions may be added. At autopsy the brain is firm and weighs 20 to 30 per cent more than is normal for the age. The dura is tense, the convolutions are flattened, and the ventricles are compressed. This condition was formerly thought to be uremia, but Volhard showed that it could occur in the presence of normal kidney function and that the term uremia is therefore incorrect.

In the majority of patients urine volume is normal throughout the acute stages. In some patients oliguria develops and may proceed to anuria. This renal shut-down is a serious manifestation. I prefer the term renal shut-down for this condition and use the term true uremia for the condition where the kidney changes are advanced and irreversible. In a few children the nephritis takes a rapidly progressive course and reaches the terminal stage (true uremia) in a short time. But in the majority of children who have impaired renal function associated with anuria during the acute stage complete recovery can and does occur. This condition is best explained on the basis of arteriolar spasm and decreased blood flow through the kidney. As Loeb points out, this idea is supported by the fact that often the anuria is terminated and diuresis appears too suddenly to be explained by the subsidence of inflammatory lesions. Some degree of edema usually goes with this condition, there is failure to concentrate and nitrogen retention and hypertension are present.

In over 60 per cent of the patients with acute glomerulonephritis there is clinical, x-ray, or electrocardiographic evidence of cardiac involvement. The incidence of electrocardiographic changes and x-ray evidence of cardiac enlargement is dependent on the frequency with which such studies are made. In a small number cardiac insufficiency may appear suddenly or develop slowly and result in death. Cardiac dilatation without histological changes is the common finding. Dyspnea or dizziness when the patient sits up, hypertension, a low pulse pressure, or the poor quality of the heart sounds and a systolic murmur may be the only clinical indications of cardiac involvement. The symptoms of cardiac failure are easily recognized.

The anatomical changes, the etiology and pathogenesis of these three conditions are not well understood. The one common factor in all of them is hypertension and the one reliable objective guide to the state of the circulation in acute nephritis is the blood pressure. I think it is impor-

tant for the clinician to realize that when hypertension is present in a child with acute nephritis there are also present these three real threats to life, the danger to the brain, the heart and the kidney.

The successful treatment of cerebral edema was developed in this country by Blackfan. The plan of treatment given here is that advocated by Blackfan and Butler and will serve as a basis for the treatment of cerebral edema, cardiac and renal failure. Any patient with a systolic blood pressure over 115 mm. of Hg., or whose blood pressure is rising, or who has any signs or symptoms of cerebral edema is given 4 to 8 cc. of 25 per cent solution of $MgSO_4$ .7 H_2O intramuscularly. The dose is repeated if the blood pressure has not fallen at the end of two hours or if the blood pressure at a later period begins to rise. With the intramuscular injection 1 to 2 ounces of 50 per cent $MgSO_4$ solution is given by mouth every four hours, until the blood pressure has remained normal for twenty-four hours or until catharsis results. If convulsions are present 1 per cent $MgSO_4$ .7 H_2O, 100 to 150 cc. may be given by vein. This form of therapy is ineffective and contraindicated in all forms of chronic nephritis with hypertension, and the diagnosis should be made before therapy is pushed. Overdosage is indicated by slow, irregular respiration; if this occurs 5 to 10 cc. of 5 per cent $CaCl_2$ should be given intravenously. The physiological action of $MgSO_4$ is not known. Experimental work by Rubin and Rappoport has shown that the inclusion of $MgSO_4$ in the diet of rats inhibits the vascular spasm produced by ergotamine tartrate in rats not so protected. Whatever the explanation empirically we know that $MgSO_4$ lowers the blood pressure, relieves intracranial pressure and increases urine volume.

With this plan of medication fluid intake should be liberal, between 1000 and 1200 cc. per twenty-four hours. The caloric needs may be disregarded until clinical improvement and a return of appetite, when a regular diet may be given. Other measures for the relief of cerebral symptoms, such as lumbar puncture, venesection, and the infusion of 50 per cent sucrose are seldom necessary. Lumbar puncture is not without danger since the sudden withdrawal of large amounts of cerebrospinal fluid in the presence of increased intracranial pressure may induce the medullary cone phase and death.

Oliguria and even complete anuria is at times a difficult problem for the clinician. I have had no experience with diathermy, radiation of the kidneys, renal denervation or decapsulation. The hunger-thirst regime

of Volhard seems to me too drastic for children. In addition to the ordinary measures taken the infusion of saline or hypertonic glucose and $MgSO_4$ intramuscularly or by mouth has seemed to induce diuresis but many times all that is necessary is a little patience.

For those children who have only slight evidence of cardiac involvement nothing more than complete bed rest is indicated. But if cardiac failure develops then in addition to $MgSO_4$ given as outlined above food and fluid should be restricted, venesection is practiced, 50 per cent glucose is given intravenously and digitalis and strophanthus may be used. Chloral hydrate and morphine are good sedatives. I feel that insuring absolute rest will accomplish more for the patient than subjecting him to many procedures of doubtful value.

The other important cause of death in acute nephritis is infection, either *per se* or as a contributory factor present in the circulatory conditions just discussed. Infection and acute nephritis are inseparable but the relationships and mechanisms are unknown. Much has been written on this subject but no one is in a position to speak with authority. For practical purposes the question divides itself into 1) the management of infections during the acute stage and 2) the problem of foci of infection.

In some cases the infection is subsiding by the time the nephritis has appeared, and only conservative therapeutic measures need be considered. But in the majority of patients there is evidence of a complication of the original infection or of a new infection. Peters states it this way: "Nephritis does not usually attack those patients who have an uncomplicated convalescence (from scarlet fever or angina) but those who have a septic complication such as cervical adenitis, otitis media, etc., from which Streptococcus can be recovered". So in some patients infection is a major problem. A mastoiditis, a peritonsillar or retropharyngeal abscess may demand immediate operation. Even if renal function is impaired and hypertension with its threat of cerebral edema and cardiac failure is present, I believe that major surgical indications in these patients should be met at the appropriate time. In these circumstances the nephritis should be regarded as an indication, not a contraindication for operation. Early in the disease we can count on enough renal and cardiac reserve to take the patient through a severe operation. These reserves may not be present if we wait too long. We have never seen harmful effects follow operations performed during the acute stages of the nephritis. Blood transfusion and specific serum therapy may be used whenever they are definitely indi-

cated. There is good clinical evidence that in the majority of cases the proper treatment of severe infection in the acute stages of nephritis has a favorable effect on the course of the disease. We have all seen dramatic improvement in the nephritis follow in a few days after a mastoid operation or the relief of a peritonsillar abscess. But it cannot be said that such measures will prevent the development of chronic nephritis. It is true that some of the children who progress to chronic nephritis have persistent or recurrent infection in spite of proper care early in the disease. But it is also true that many children who have persistent or recurrent infection never develop chronic nephritis. I can only say that adequate surgical treatment of infection in patients with acute glomerulonephritis is fully justified on theoretical and clinical considerations. In my experience this practice has given uniformly favorable results; neglect has been disastrous.

We have used sulfanilamide in a few cases of nephritis with active streptococcus infection. The only thing I can say about it is that if renal function is impaired the level of sulfanilamide in the blood must be carefully watched. Nor can it be stated that the use of this drug early in the course of streptococci infections will prevent the development of acute nephritis.

The problem of foci of infection in children with acute nephritis usually comes down to the questions: 1) Should tonsillectomy be performed? and 2) If so, when is the best time to do it? All agree that the usual indications for tonsillectomy are more easily accepted in a child with nephritis. My own belief is that acute glomerulonephritis is an indication for tonsillectomy. In hospital practice is seems to me a much safer plan to operate on all children. In private practice other circumstances may justify a more conservative policy. But I have not yet learned how to tell what is at the bottom of a tonsil by looking at the outside. Since history, examination, and laboratory tests may be so misleading it would seem much safer to have the tonsils out in any event.

There is a general belief that tonsillectomy should not be done during the acute stages of glomerulonephritis. Some authorities wait for complete recovery or until improvement has stopped. It seems to me that in the ordinary case the time for tonsillectomy is when the hematuria and albuminuria have diminished, when hypertension has subsided, and most important, when the throat is not acutely inflamed. No rule can be made, but in the majority of patients this point is reached in the first two to four months after the onset of acute nephritis. In certain cases there are definite

indications for early tonsillectomy. When during the first few weeks of the disease the nephritis does not improve on a suitable regime, and the otitis or mastoid do not heal as promptly as expected, and when there are repeated attacks of pharyngitis with adenitis with or without exacerbation of the nephritis, tonsillectomy should be considered and performed at the earliest opportunity despite the activity of the nephritis. Parsons and Barling state that "On general principles a focus which is definitely septic (e.g., tonsils) should be removed as soon as possible; but each case must be considered as an independent problem. Operations should not be undertaken during an acute attack of glomerulonephritis without very serious thought; but the general reaction is often surprisingly slight, and the practice is to be commended if the focal inflammation is quite definite and improvement in the kidney trouble is not taking place. There is of course the danger of a very considerable reaction".

The objections to this early attack on foci of infection are in general that it makes the patients worse and specifically that it causes a flare-up in the urine. But if one studies these patients carefully it is seen that the postoperative flare-up is mild and transient and is not accompanied by hypertension or edema, whereas a recurrence of the infection is usually accompanied by a real exacerbation of the nephritis. In my experience I have not seen the evil results predicted by those who have not followed this plan, and therefore this criticism of early tonsillectomy seems invalid.

I admit that we are ignorant of the mechanisms involved, and that no one can say that early tonsillectomy lessens the incidence of infection or prevents chronic nephritis. In considering this problem the following facts seem pertinent: 1) No one can tell which acute cases will progress to chronic nephritis, 2) Acute nephritis is almost invariably preceded and accompanied by upper respiratory infection or one of its complications, 3) Recurrent infection in the convalescent period has an unfavorable effect on the nephritis, 4) The development of chronic nephritis is at times associated with persistent or recurrent infection, 5) When chronic nephritis has become established any attack on foci of infection is useless. These facts lead naturally to the conclusion that anything we can do to fight a condition so closely related to acute and chronic nephritis should be done and done as early as possible. Only long continued observation will bring satisfactory proof; meanwhile one's clinical experience is worth something. In our hands this plan of management has not been harmful and so far the results justify its continuance.

In closing I realize I have omitted to say anything about the general measures taken in the management of acute nephritis. This is not because I think them unimportant but because I think they are well covered in the texts on the subject. I have stressed the problems of infection and circulatory disturbances in acute nephritis in children because they are inadequately treated in most text books and are neglected by many clinicians. My only excuse for spending so much time on the subject is the belief that if the physician will realize these serious possibilities inherent in a child ill with nephritis a more alert attitude will result in a lowered mortality.

LIBRARY NOTES

A SELECTED LIST OF PERIODICALS ADDED IN 1937

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Acta Neerlandica morphologiae normalis et pathologicae.
Utrecht, Vol. 1, No. 1, 1937.

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London, Vol. 1, No. 1, May 1937.

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Bucuresti, Anul 1, No. 1, Dec. 1936.

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Roma, Anno 1, No. 1, Jan. 1937.

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Dresden und Leipzig, Band 1, Heft 1/6, July 1937.

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N. Y., Vol. 1, No. 1, March 1937.

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Journal of Parapsychology.
Durham, N. C., Vol. 1, No. 1, March 1937.

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Beacon, N. Y., Vol. 1, No. 1/2, July-Oct. 1937.

Studies of the Institutum Divi Thomae; published by Institutum Divi Thomae of the Athenaeum of Ohio.
Cincinnati, Vol. 1, No. 1, 1937.

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Istanbul, Yil 1, Sayi 1, Feb. 1936.

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Contributions from the Institute of Physiology, National Academy of Peiping. Peiping.

Diseases of the Chest. El Paso, Texas.

Journal of Dairy Research. London.

Journal of the Royal Army Veterinary Corps. Aldershot, England.

Medizinmechanik. Berlin.

Monatshefte für Chemie. Leipzig und Wien.

Monitore ostetrico-ginecologico. Modena.

Neopsichiatria; rassegna di psichiatria—neurologia—endocrinologia. Pisa.

Pacific Coast Journal of Homoeopathy. San Francisco.

Plant Physiology. Lancaster, Pa.

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Rassegna italiana d'ottalmologie. Torino.

Revista paulista de tisiologia. São Paulo.

Revue belge de la tuberculose. Bruxelles.

Revue v neurologii a psychiatrii. Praha.

Thalès; recueil annuel des travaux de l'Institut d'histoire des sciences et des techniques de l'Université de Paris. Paris.

University of Toronto Studies, Child Development Series. Toronto.

RECENT ACCESSIONS

"Possession does not imply approval"

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Bourdelle, E.; Bennejeant, C. & Wicart, A. E. *Anatomie et physiologie bucco-dentaires.* Paris, Baillière, 1937, 614 p.

Braude, M. *The principles and practice of clinical psychiatry.* Phil., Blakiston, [1937], 382 p.

Clark, G. N. *Science and social welfare in the age of Newton.* Oxford, Clarendon Press, 1937, 159 p.

Davison, A. *Mammalian anatomy, with special reference to the cat.* 6. ed. Phil., Blakiston, [1937], 328 p.

Eggleston, C. *Essentials of prescription writing.* 6. ed. Phil., Saunders, 1938, 155 p.

Elbel, H. *Die wissenschaftlichen Grundlagen der Beurteilung von Blutalkoholbefunden.* Leipzig, Thieme, 1937, 106 p.

Geckeler, E. O. *Fractures and dislocations.* Balt., Wood, 1937, 252 p.

Globus, J. H. *Practical neuroanatomy.* Balt., Wood, 1937, 387 p.

Hurst, (Sir), A. F. *The time has come . . . The Harveian oration . . . 1937.* London, Headley, [1938?], 42 p.

Kessler, W. *Kinder-Zahnheilkunde.* 2. Aufl. München, Lehmann, 1937, 292 p.

Kolmer, J. A. & Boerner, F. *Approved laboratory technic.* 2. ed.
N. Y., Appleton-Century, [1938], 893 p.

Leonhard, K. *Involutive und idiopathische Angstdepression in Klinik und Erblichkeit.*
Leipzig, Thieme, 1937, 116 p.

Madaus, G. *Lehrbuch der biologischen Heilmittel. Abt. 1: Heilpflanzen.*
Leipzig, Thieme, 1938, 4 v.

Maxwell, J. T. *Outline of ocular refraction.*
Omaha, Medical Pub. Co., 1937, 395 p.

Milestones in medicine; laity lectures of the New York Academy of Medicine.
N. Y., Appleton-Century, 1938, 276 p.

Müller, W. *Die angeborenen Fehlbildungen der menschlichen Hand.*
Leipzig, Thieme, 1937, 170 p.

National League of Nursing Education. Curriculum Committee. *A curriculum guide for schools of nursing.* 2. revision.
N. Y., Nat. League of Nursing Educ., 1937, 689 p.

Padgett, E. C. *Surgical diseases of the mouth and jaws.*
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Rice, C. O. *Injection treatment of hernia.*
Phil., Davis, 1937, 266 p.

Riesman, D. *High blood pressure and longevity, and other essays.*
Phil., Winston, [1937], 726 p.

Sauerbruch, F. & O'Shaughnessy, L. F. *Thoracic surgery.*
London, Arnold, 1937, 394 p.

Scheid, K. F. W. *Febrile Episoden bei schizophrenen Psychosen.*
Leipzig, Thieme, 1937, 97 p.

Schweitzer, Alfred. *Die Irradiation autonomer Reflexe.*
Basel, Karger, 1937, 375 p.

Stärke, W. *Paradentose.*
München, Lehmann, 1937, 280 p.

Stitt, E. R.; Clough, P. W. & Clough, (Mrs.) M. (Clark). *Practical bacteriology, haematology and animal parasitology.* 9. ed.
Phil., Blakiston, [1938], 961 p.

Vannotti, A. *Porphyrine und Porphyrinkrankheiten.*
Berlin, Springer, 1937, 286 p.

Winslow, C. E. A. & Zimand, S. *Health under the "El"; the story of the Bellevue-Yorkville Health Demonstration.*
N. Y., Harper, 1937, 203 p.

PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

March 3—*The New York Academy of Medicine.* Executive Session—a] Reading of the minutes. ¶ Presentation of the Academy Medal to Dr. Bela Schick on the occasion of the twenty-fifth anniversary of the publication of his work on immunity in diphtheria. ¶ Papers of the evening—a] The recognition of deficiencies in the first four vitamins and measures for prevention, Edwards A. Park, Pediatrician-in-Chief, The Johns Hopkins Hospital, Baltimore; b] The specific prevention of diphtheria—further observations and inquiries, John G. FitzGerald, Director, School of Hygiene and Connaught Laboratories, University of Toronto; c] Variations in incidence in infectious diseases, James Payton Leake, U. S. Public Health Service Bureau.

March 17—*The Harvey Society (in affiliation with The New York Academy of Medicine).* The sixth Harvey Lecture, The Isolation and Properties of Tobacco Mosaic and Other Virus Proteins, Wendell M. Stanley, Associate Member, The Rockefeller Institute, Princeton.

SECTION MEETINGS

MARCH 1—*Section of Dermatology and Syphilology.* Reading of the minutes. ¶ Presentation of cases—a] New York University, College of Medicine; b] Miscellaneous cases. ¶ Discussion of selected cases. ¶ Executive session.

MARCH 1—*Joint Meeting of the Section of Neurology and Psychiatry and the New York Neurological Society.* Reading of the minutes. ¶ Papers of the evening—a] Ephedrine in the treatment of convulsive seizures, Israel S. Wechsler; Discussion by Foster Kennedy, S. Bernard Wortis, George Hyslop, Emanuel D. Friedman, Israel Strauss; b] Surgical therapy in certain convulsive disorders, Ira Cohen; Discussion, Charles A. Elsberg, Joseph H. Globus, John H. Scarff, Israel Strauss; c] Perverse tendencies and fantasies—their influence on personality, Sandor Lorand; Discussion by Abraham A. Brill, Israel Strauss, Clarence Oberndorf, Foster Kennedy. ¶ Executive session.

MARCH 9—*Section of Historical and Cultural Medicine.* Executive session—a] Reading of the minutes; b] Nomination of section officers and one member of advisory committee. ¶ Papers of the evening—a] Peter Dettweiler (1837-1937) initiator of the rest cure in tuberculosis, S. Adolphus Knopf; b] Niels Stensen—his tercentenary, Anne Tjomsland. ¶ General discussion.

MARCH 10—*Section of Pediatrics.* Case report; Feeding the cleft palate infant with the aid of a dental plate, J. H. Sillman, D.D.S. (by invitation). ¶ Papers of the evening—a] A preliminary study of stimulation of growth in short normal children and dwarfs, Josephine H. Kenyon; Discussion by Irving H. Pardee; b] The anaphylactogenic properties of cereal foods and breadstuffs, Bret Ratner; Discussion by Oscar M. Schloss; c] Bulbar poliomyelitis following tonsillectomy and adenoidectomy, Alfred E. Fischer, Maxwell Stillerman (by invitation); Discussion by Sidney D. Kramer (by invitation); d] The diagnosis of blood dyscrasias by sternal marrow puncture, Peter Vogel (by invitation), Frank A. Bassen (by invitation); Discussion by Nathan Rosenthal.

MARCH 15—*Combined Meeting of the Section of Medicine and the Section of Surgery.* Executive session—a] Reading of the minutes; b] Appointment of nominating committee, section of medicine; c] Appointment of nominating committee, section of surgery. ¶ Papers of the evening—a] Physiology and pathology of extracellular fluid, James L. Gamble, Boston (by invitation); Discussion by A. A. Weech (by invitation), Dana W. Atchley; b] Simple and accurate blood studies in surgical emergencies (shock, hemorrhage, trauma, burns, perforations, intestinal obstruction) as a guide to appropriate and adequate therapy, John Scudder (by invitation); Discussion by William F. MacFee, Samuel Standard. ¶ General discussion.

MARCH 16—*Section of Genito-Urinary Surgery.* ¶ Executive session—a] Reading of the minutes; b] Appointment of nominating committee. ¶ Presentation of cases—The present status of cystometry, with special reference to microcystometry, Irving Simons. ¶ Paper of the evening—Ureteral transplantation: A resume of the indications and contraindications and personal experiences with the operation, Elmer Hess, Erie, Pa. (by invitation). ¶ General discussion, Simon A. Beisler, Abraham Hyman, Thomas J. Kirwin.

MARCH 16—*Section of Otolaryngology.* This meeting held conjointly with the Section of Otolaryngology of the College of Physicians of Philadelphia. Reading of the minutes. ¶ Papers of the evening—a] Parapharyngeal hemorrhages, diagnosis and treatment, Louis Hubert, Francis W. White; Discussion by Warren B. Davis (by invitation); b] Treatment of carcinoma of the larynx, Rudolph Kramer; Discussion by Gabriel

Tucker (by invitation); c] Modification of the semilunar ganglion approach used in surgery of petrous pyramid, Marvin F. Jones; Discussion by Oscar V. Batson (by invitation). ¶ General discussion.

MARCH 18—*Section of Orthopedic Surgery.* Executive session—a] Reading of the minutes; b] Appointment of nominating committee. ¶ Papers of the evening—a] Painful hips, M. N. Smith-Petersen, Boston (by invitation) (45 minutes); b] Bone block for painful hips, Joseph B. L'Episcopo (30 minutes); c] Discussion, Philip D. Wilson, Nicholas S. Ransohoff, Alan DeForest Smith. ¶ General discussion.

MARCH 21—*Section of Ophthalmology.* Display of mammalian fundus plates—Demonstration of materials, methods and technique of art in relation to eye by various ophthalmologists and artists. ¶ Executive session (8:30)—a] Reading of the minutes; b] Appointment of nominating committee. ¶ a] Art in ophthalmology, Percy Fridenberg (by invitation); b] Mammalian fundi, LeGrand H. Hardy. ¶ Presentation of cases—a] Choroidal hemorrhage simulating a choroidal tumor, Martin Cohen, Lewis W. Crigler; b] An unusual case of retinal detachment with cyst formation, Walter Griffey (by invitation); c] Plastic repair of old laceration of lower lid (moving picture demonstration), Wendell L. Hughes. ¶ Paper of the evening—A preliminary report of the value of functional visual tests for the localization of supratentorial tumors of the brain (illustrated by lantern slides), Charles A. Elsberg, Hyman Spotnitz (by invitation); Discussion, John M. Wheeler.

MARCH 22—*Section of Obstetrics and Gynecology.* From the Memorial Hospital. Executive session — Appointment of nominating committee. ¶ Papers of the evening—a] Experience with radium therapy alone in cancer of the corpus uteri, Robert L. Brown (by invitation); Discussion, Nelson B. Sackett; b] Management of the advanced case of carcinoma of the cervix, E. L. Frazell (by invitation); Discussion, Ira I. Kaplan; c] Chorio-carcinoma, a report of seven cases, John A. Kelly (by invitation); Discussion, Thomas C. Peightal; d] Choice of treatment in fibromyoma of the uterus, William P. Healy; Discussion, James A. Corscaden.

AFFILIATED SOCIETIES

MARCH 16—*New York Section of the Society for Experimental Biology and Medicine at The New York Academy of Medicine, 2 East 103 Street.* Vitamin B_1 metabolism in man. Urinary excretion of B_1, Alfred S. Schultz, Robert F. Light, Charles N. Frey (introduced by I. Greenwald). ¶ The effect of choline on the production of experimental atherosclerosis in rabbits, Alfred Steiner (introduced by Kenneth B. Turner). ¶ Investigations on the pathogenesis of tetanus, Bernard Zuger, Ulrich Friedemann (introduced by Benjamin Kramer). ¶ Hemolytic properties of indol, Eric Ponder. ¶ The diagnosis of venous-arterial shunt by the ether circulation time method, William Benenson, William M. Hitzig (introduced by George Baehr). ¶ Effect of cyclopropane on intestinal activity in vivo, C. L. Burstein (introduced by CoTui).

MARCH 21—*The New York Roentgen Society in affiliation with The New York Academy of Medicine.* Presentation of interesting cases. ¶ Paper of the evening—Cancer of head and neck, Douglas Quick; Discussion, Hayes Martin (by invitation), William Harris, Maurice Lenz. ¶ Executive session.

MARCH 29—*New York Pathological Society in affiliation with The New York Academy of Medicine. Joint meeting with the New York Gastroenterological Association.* Papers of the evening—a] Heredity in cancer, Madge T. Macklin; b] Experimental evidence on the relation between heredity and external factors in cancer, Clara Lynch.

DEATHS OF FELLOWS

CHARD, MARIE LOUISE: 121 East 60 Street, New York City; born in Brooklyn, New York, January 6, 1868; died in New York City, January 20, 1938; graduated in medicine from the Women's Medical College of the New York Infirmary for Women and Children in 1895; elected a Fellow of the Academy May 5, 1904.

Dr. Chard was consulting surgeon and gynecologist to the New York Infirmary for Women and Children and a member of the Board of Trustees of that institution.

Dr. Chard was a Fellow of the American College of Surgeons, the American Medical Association, and a member of the County and State Medical Societies.

EDGERTON, FRANCIS CRUGER: 570 Park Avenue, New York City; born in Middletown, Connecticut, July 11, 1874; died in New York City, February 19, 1938; graduated in medicine from the College of Physicians and Surgeons in 1898; elected a Fellow of the Academy November 5, 1903.

Dr. Edgerton was consulting surgeon to the St. Mary's Hospital in Hoboken. He was a Fellow of the American Medical Association, the American College of Surgeons and a member of the International Society of Urology, the American Association of Genito-Urinary Surgeons, and the County and State Medical Societies.

GELBER, CHARLES NEUMAN: 30 East 40 Street, New York City; born in Austria, June 2, 1891; died in New York City, March 3, 1938; graduated in medicine from the Long Island College of Medicine in 1913; elected a Fellow of the Academy, November 3, 1921.

Dr. Gelber was a Fellow of the American Medical Association and a member of the County and State Medical Societies.

MICHAELIS, ALFRED: 171 West 71 Street, New York City; born in Berlin, Germany, February 11, 1874; died in New York City, January 29, 1938; received the degree of Bachelor of Arts from the College of the City of New York in 1894 and graduated in medicine from the College of Physicians and Surgeons in 1898; elected a Fellow of the Academy February 7, 1907.

Dr. Michaelis was Assistant Professor of Otolaryngology at the College of Physicians and Surgeons and Attending Neurologist to the Vanderbilt Clinic. He was a Fellow of the American Medical Association and a member of the County and State Medical Societies.

SCHROEDER, LOUIS CLAUSEN: 50 East 72 Street, New York City; born in Philadelphia, Pennsylvania, April 14, 1881; died in New York City, February 25, 1938; graduated in medicine from the College of Physicians and Surgeons in 1911; elected a Fellow of the Academy, February 7, 1918 and designated a Fellow in Pediatrics in 1933.

Dr. Schroeder was attending physician to the New York Hospital and consulting physician to the St. Luke's, Newburgh and State Reconstruction Hospitals. He was Assistant Professor of Clinical Pediatrics at Cornell University Medical College.

Dr. Schroeder, who held a certificate from the American Board of Pediatrics, was a Fellow of the American Medical Association and a member of the American Pediatric Society, the American Academy of Pediatrics and the County and State Medical Societies. He was a member of the Editorial Board of Preventive Medicine.